Asymmetric Synthesis of Secondary and Tertiary Boronic Esters

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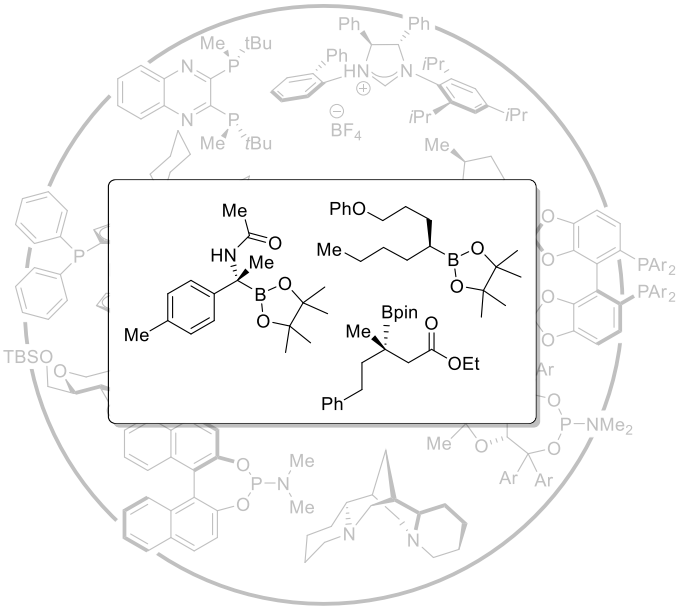
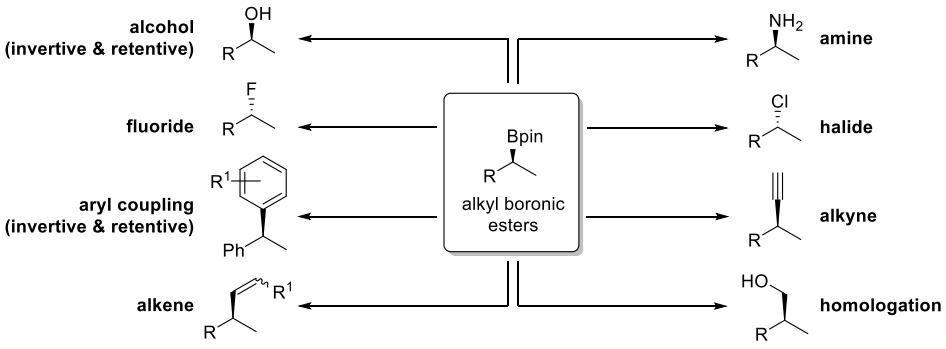
Abstract:

Non-racemic chiral boronic esters are recognised as immensely valuable building blocks in modern organic synthesis. Their stereospecific transformation into a variety of functional groups – from amines and halides to arenes and alkynes – along with their air and moisture stability, has established them as an important target for asymmetric synthesis. Efforts towards the stereoselective synthesis of secondary and tertiary alkyl boronic esters have spanned over five decades and are underpinned by a wealth of reactivity platforms, drawing on the unique and varied reactivity of boron. This review summarizes strategies for the asymmetric synthesis of alkyl boronic esters, from the seminal hydroboration methods of H. C. Brown to the current state of the art.



1. *Introduction*

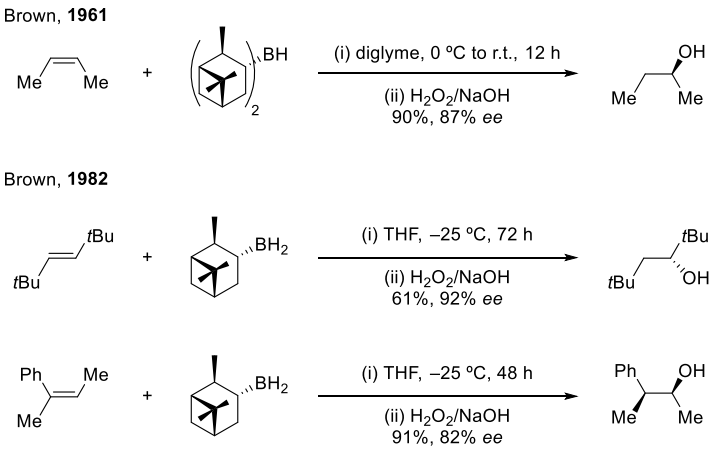
Organoboron compounds are highly versatile intermediates in synthesis. Herbert C. Brown's breakthrough in asymmetric hydroboration fuelled a major program focused on developing protocols for transforming organoborane intermediates into a range of useful functional groups. Whilst successful, the air and moisture sensitivity of the organoboranes mitigated against their greater uptake in the community. In contrast, boronic esters are air and moisture stable making them easier to handle and manipulate. This increased stability derives from π donation of electron density from the oxygen atoms into the empty p orbital on boron, thus reducing the electrophilicity of the boron centre and its propensity to undergo oxidative or radical decomposition processes. Furthermore, a growing repertoire of stereospecific transformations have been developed that enable the conversion of enantioenriched secondary and tertiary boronic esters into a broad range of functional groups (Scheme 1). Thus, combining methods that introduce boronic esters into organic molecules with high stereocontrol and methods for their stereospecific transformation provides a powerful platform for asymmetric synthesis. This review focuses on asymmetric methods for the introduction of boronic esters into organic molecules, but includes some of the ground-breaking work on boranes for historical purposes. It covers reports up to January 2017.



Scheme 1: *Selected stereospecific transformations of alkyl boronic esters.*

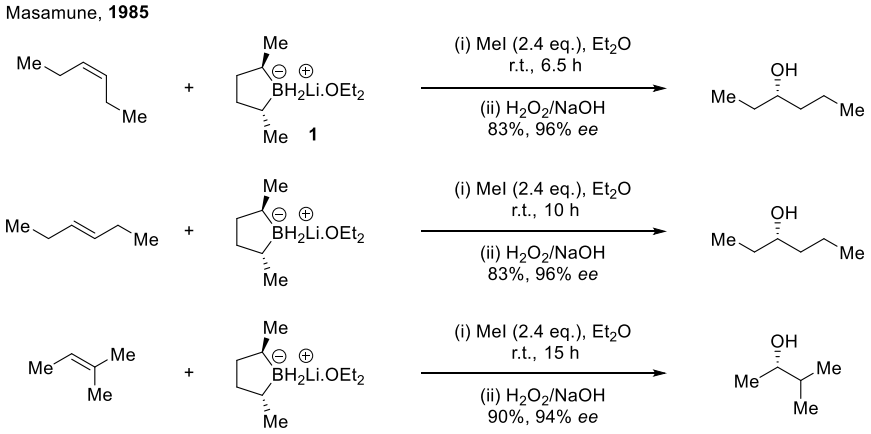
2. *Non-Metal-Catalysed Hydroboration of Alkenes*

In 1961, Brown and Zweifel reported the first synthesis of non-racemic chiral alkyl boronic esters, initiating a field of research that has remained at the forefront of synthetic chemistry for over fifty years.[1] Describing one of the earliest non-enzymic transformations to provide organic molecules in significant levels of enantioenrichment, they disclosed the asymmetric hydroboration of alkenes using diisopinocampheylborane (Ipc_2BH), a dialkylborane itself derived from the hydroboration of α-pinene. Using Ipc_2BH, Brown and Zweifel detailed the asymmetric hydroboration of 1,2-*cis* substituted alkenes; following oxidation, alcohols could be accessed in unprecedented levels of enantioenrichment (83–91% *ee*, Scheme 2). Despite these remarkable findings, extension of this methodology to other classes of alkene, namely 1,2-*trans*-disubstituted, 1,1-disubstituted, and trisubstituted alkenes led to unsatisfactory levels of asymmetric induction. Over the following years, Brown and co-workers not only developed methods for the synthesis of the reagent, Ipc_2BH, in higher levels of optical purity (leading to higher levels of asymmetric induction in the hydroboration reaction of 1,2-*cis*-disubstituted alkenes)[2], but also discovered that monoisopinocampheylborane ($IpcBH_2$) could hydroborate both 1,2-*trans*-disubstituted alkenes and trisubstituted alkenes with considerably higher levels of asymmetric induction. Ipc_2BH, however, remains the reagent of choice for the effective asymmetric hydroboration of 1,2-*cis*-disubstituted alkenes.[3,4,5]



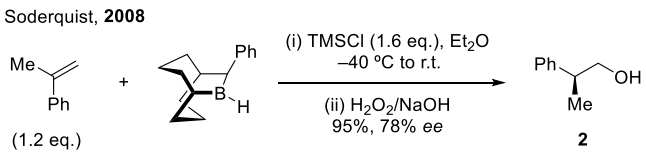
Scheme 2: *Brown's alkene hydroboration using Ipc_2BH and $IpcBH_2$.*

In 1985, Masamune and co-workers introduced C_2-symmetric borane reagent **1** (Scheme 3).[6] This reagent could hydroborate all three previously addressed classes of alkene in high levels of enantioenrichment. Although the levels of asymmetric induction were often higher than those of the α-pinene derived reagents developed by Brown, the synthesis of this C_2-symmetric borane was lengthy and has thus failed to compete.



Scheme 3: *Masamune's alkene hydroboration.*

Since Brown's first disclosure in 1961, it took almost fifty years for a solution to the long-standing problem of 1,1-disubstituted alkenes to appear. In 2008, Soderquist and co-workers reported a new class of borane reagent, the 10-substituted-9-borabicyclo[3.3.2]decanes (10-R-9-BBD-H).[7] This reagent was not only simple to access by resolution with pseudoephedrine, but led to unprecedented levels of asymmetry, for example, providing **2** in 78% *ee* (previous levels of enrichment reached about 10%).



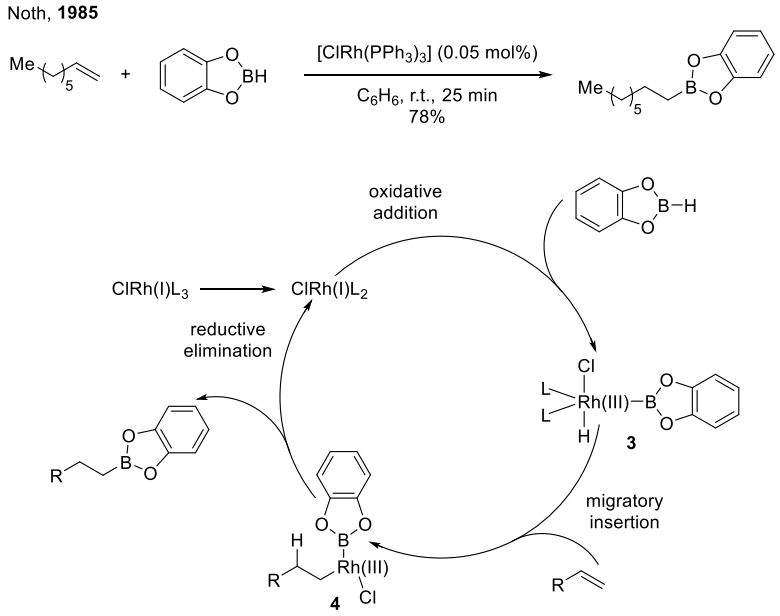
Scheme 4: *Soderquist's hydroboration of 1,1-disubstituted alkenes.*

The non-metal-catalysed hydroboration of alkenes, pioneered throughout the second half of the twentieth century by Brown and co-workers, describes an important period in the history of synthetic chemistry, marking the rise of asymmetric synthesis. Despite impressive developments in the levels of

enantioselectivity that can be obtained in hydroboration reactions of all four classes of alkene, a number of limitations remained including functional-group compatibility and the necessity of using symmetrical internal alkenes to avoid issues of regioselectivity. By the time Soderquist had finally addressed the problem of 1,1-disubstituted alkenes, catalytic methods, proceeding through a wealth of reactivity platforms, had already established themselves as enticing alternatives, often offering greater generality, complementary chemo- and regioselectivities and higher levels of asymmetric induction.

3. *Transition Metal-Catalysed Hydroboration of Alkenes*

A major breakthrough in the stereoselective synthesis of alkyl boronic esters came with the report by Nöth and Männig in 1985 that the hydroboration of alkenes with catecholborane could be catalysed by the neutral rhodium(I) complex, Wilkinson's complex $[ClRh\{P(C_6H_5)_3\}_3]$.[8] This discovery marked an alternative mechanistic pathway for the transfer of both components of a borane species across an alkene. While the work on non-catalysed transformations over the previous twenty years harnessed the electrophilicity of the empty p orbital on boron to facilitate attack by the π-system of the alkene, the introduction of a rhodium complex diverted the reactivity along a completely different pathway. Nöth and Männig proposed a mechanism involving the oxidative addition of catecholborane to the rhodium(I) centre to give rhodium(III) complex **3** (Scheme 5). Alkene association followed by insertion into the rhodium(III)–hydride bond provides rhodium(III)–alkyl species **4**. Reductive elimination of the carbon–boron bond then releases the alkyl boronic ester and regenerates the active rhodium(I) species primed for subsequent oxidative addition into the boron–hydride bond. This mechanism was supported by a report by Kono and Ito ten years previously, describing the oxidative addition of Wilkinson's catalyst into the boron–hydrogen bond of catecholborane to give the rhodium–hydride complex, $[RhClH(BO_2C_6H_4)(PPh_3)_2]$.[9]

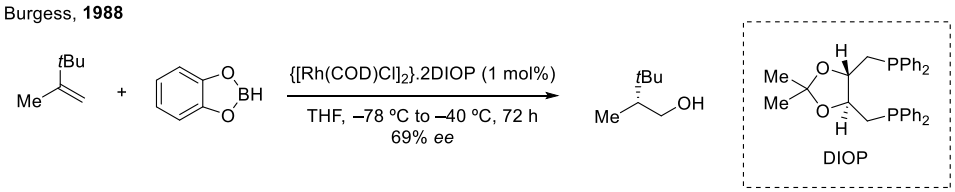


Scheme 5: *Rhodium-catalysed alkene hydroboration with catecholborane.*

Remarkable, and highly synthetically valuable, chemoselectivity was observed in this rhodium-catalysed process: in the presence of the rhodium(I) catalyst, a terminal alkene underwent hydroboration selectively in the presence of a ketone, in direct contrast with the non-catalysed process. Although the catalysed process exhibited levels of chemoselectivity that were different from those of the non-catalysed process, it exhibited the same regioselectivity, delivering the anti-Markovnikov primary alkyl boronic ester.

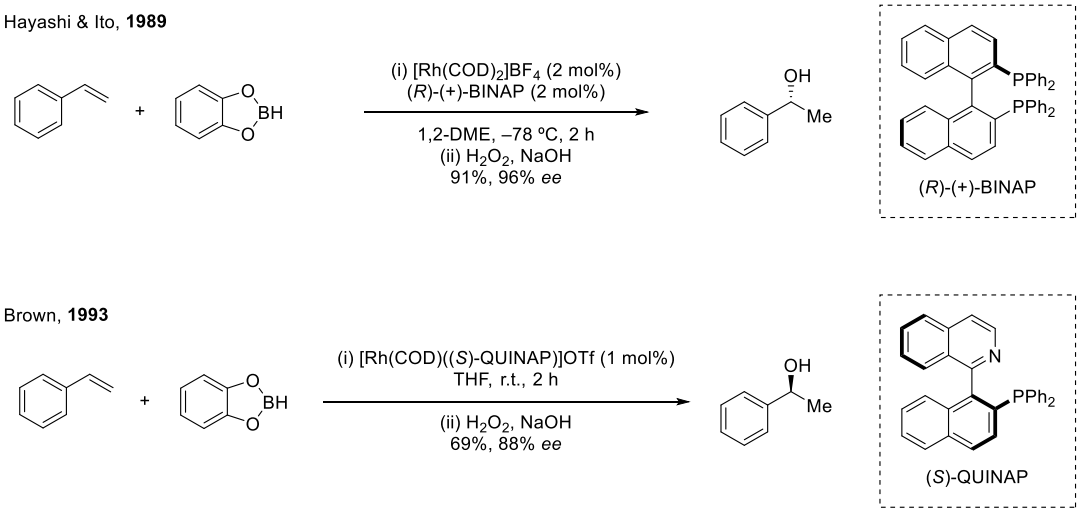
In 1988, Burgess and Ohlmeyer reported the first enantioselective rhodium(I)-catalysed hydroboration of alkenes through the introduction of homochiral diphosphine ligands DIOP and BINAP[10] (both of which had been well established in the rhodium(I)-catalysed hydrogenation, hydroformylation and hydrosilylation of alkenes).[11,12] High reactivity was observed for this system with strained internal alkene, norbornene, with moderate temperature-dependant levels of enantioselectivity, reaching 57% *ee* when the reaction was performed at –20 °C. Internal alkenes, *E*- and *Z*-1,2-diphenylprop-1-ene, underwent the desired hydroboration in quantitative yields, but stereoselectivity was poor (up to 19% *ee* for the *Z* isomer and no evidence of stereocontrol for the *E* isomer). Important, however, were the results obtained for 1,1-disubstituted alkenes, a class of alkenes that had long posed problems for the non-catalysed process (see above). 2,3,3-Trimethylprop-1-ene provided the anti-Markovnikov

hydroboration product in 69% *ee* (Scheme 6). Suzuki and co-workers later reported similar results by using related rhodium-phosphine complexes, with enantioselectivities reaching 75% *ee*.[13,14] Also, during this period, the groups of Evans and Burgess both published extensive studies into substrate-controlled diastereoselective rhodium-catalysed hydroboration reactions of allylic alcohols and amines, reporting types of regioselectivity that were, for many substrates, complementary to the non-catalysed process.[15,16,17,18,19]



Scheme 6: *Asymmetric rhodium-catalysed alkene hydroboration.*

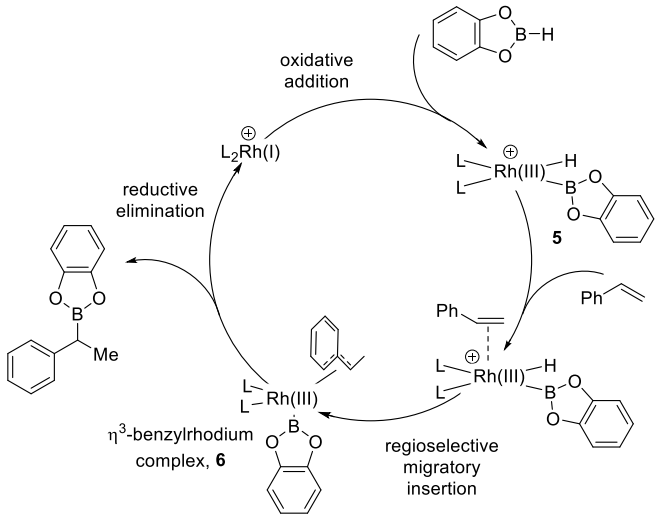
Synthetically useful levels of enantioselectivity for the rhodium-catalysed hydroboration of styrene derivatives was reported by Hayashi and Ito in 1989.[20] A cationic rhodium/BINAP system exhibited regioselectivity opposite to that obtained with the non-catalysed process (that is, the Markovnikov addition products, chiral 1-arylalkanols) and high asymmetric induction, providing the optically active secondary alcohols (following oxidation of the alkyl boronic esters) with *ee* values of up to 96% (Scheme 7). The introduction of P,N ligands by Brown and co-workers was a further important development, allowing access to the benzylic secondary alcohol products in excellent levels of enantioselectivity, notably under non-cryogenic conditions (Scheme 7).[21,22]



Scheme 7: *Asymmetric cationic rhodium-catalysed hydroboration of styrene derivatives.*

A number of important observations led to further insight into the mechanism of this process.[23] Although high Markovnikov selectivity was observed when cationic rhodium complexes were used in combination with tertiary phosphine ligands, the corresponding primary alkyl boronic esters were produced selectively in the presence of neutral rhodium complexes, such as Wilkinson's complex $[ClRh\{P(C_6H_5)_3\}_3]$. In the absence of phosphine ligands, mixtures of the primary and secondary hydroboration products were observed. Also, the transformation of β-substituted styrenes gave the benzylic boronic esters with excellent levels of selectivity when subjected to the cationic rhodium/tertiary phosphine catalyst system. The catalytic hydroboration of alkyl olefins, however, produced a mixture of the two products, a selectivity of 92:8 in favour of the primary boronic ester (this is a similar selectivity to that observed in the non-catalysed case). These observations led Hayashi and Ito to invoke the mechanism outlined in Scheme 8. In line with the mechanism proposed by Nöth and Männig, oxidative addition of catecholborane to the rhodium(I) centre generates rhodium(III)–hydride species **5**, followed by the insertion of the alkene into the rhodium–hydride bond. They postulate that, for styrene derivatives, this insertion occurs regioselectively to place the rhodium centre at the benzylic position, allowing for the formation of stabilised η^3-benzylrhodium complex **6**, from which reductive elimination provides the secondary alkyl boronic ester. They further note that such a process is only

possible for the cationic complex, which has a vacant coordination site facilitating the formation of the η^3-benzyl complex. The corresponding neutral complex, which lacks this site, is unable to form the stabilised η^3-benzyl complex, thus leading to anti-Markovnikov selectivity, which is presumably dictated by steric factors. The transformation of 1,1-disubstituted styrenes provided the primary alkyl boronic esters, even when using the cationic rhodium/tertiary phosphine system, where steric factors are likely to disfavour the formation of a tertiary rhodium–alkyl species.



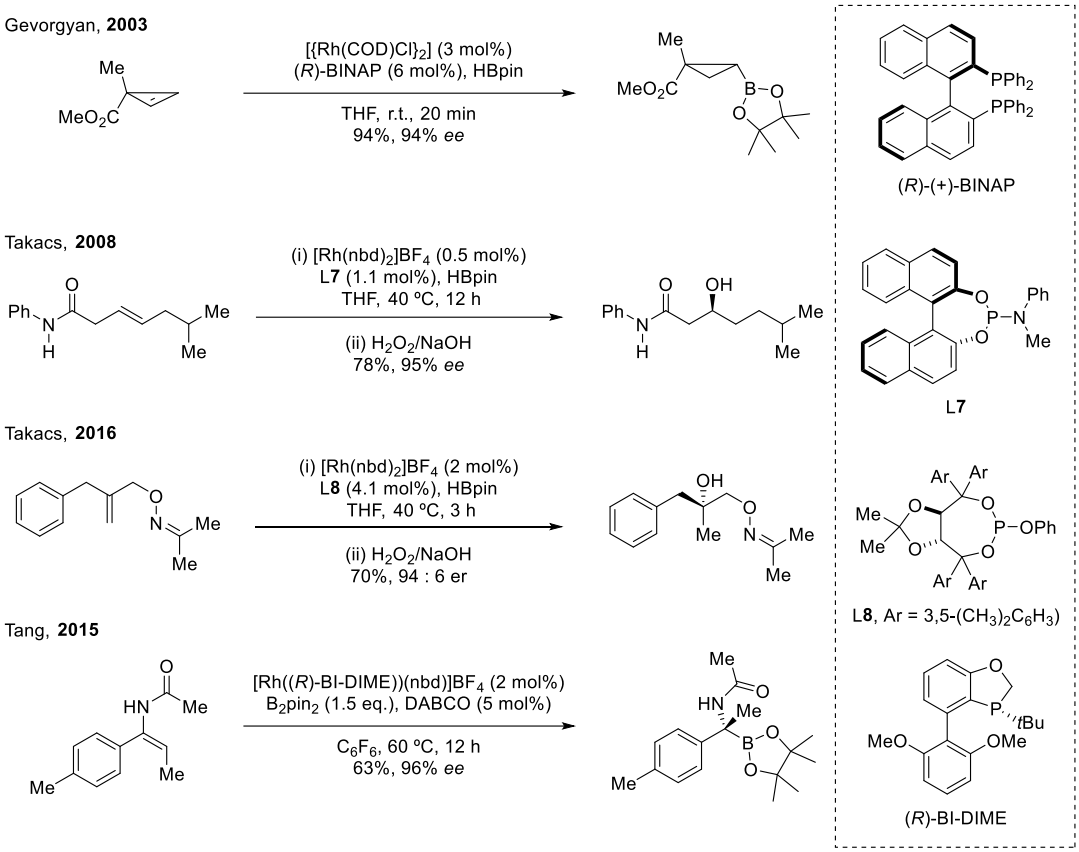
Scheme 8: *Mechanistic rational for cationic rhodium-catalysed hydroboration of styrene derivatives.*

Over the next fifteen years, many other rhodium-based systems were developed for the asymmetric hydroboration of styrene derivatives.[24] Although moderate to excellent asymmetric induction was observed for a range of P,P- and P,N ligands, general application of this process to other non-styryl alkenes was limited. Furthermore, rhodium-catalysed hydroboration of 1,1-β-disubstituted styrene derivatives reverted to anti-Markovnikov regioselectivity, preventing the development of methods for the synthesis of valuable enantioenriched tertiary alkyl boronic esters.

Expansion of the scope of transition-metal-catalysed asymmetric hydroboration arrived with a report from Evans and co-workers describing the iridium-catalysed hydroboration of β,γ-unsaturated amides; complete regiocontrol was observed providing the β-boryl products with complete selectivity (over the

γ-isomers). This regiocontrol was attributed to the directing ability of the amide functionality, through a two-point binding of the iridium centre to the amide and the alkene.[25,26,27] While non-stereoselective, these reports opened up the field of directed transition-metal-catalysed hydroboration methods, which have considerably expanded the scope of enantioenriched alkyl boronic esters available beyond symmetrical internal alkene substrates (see below).

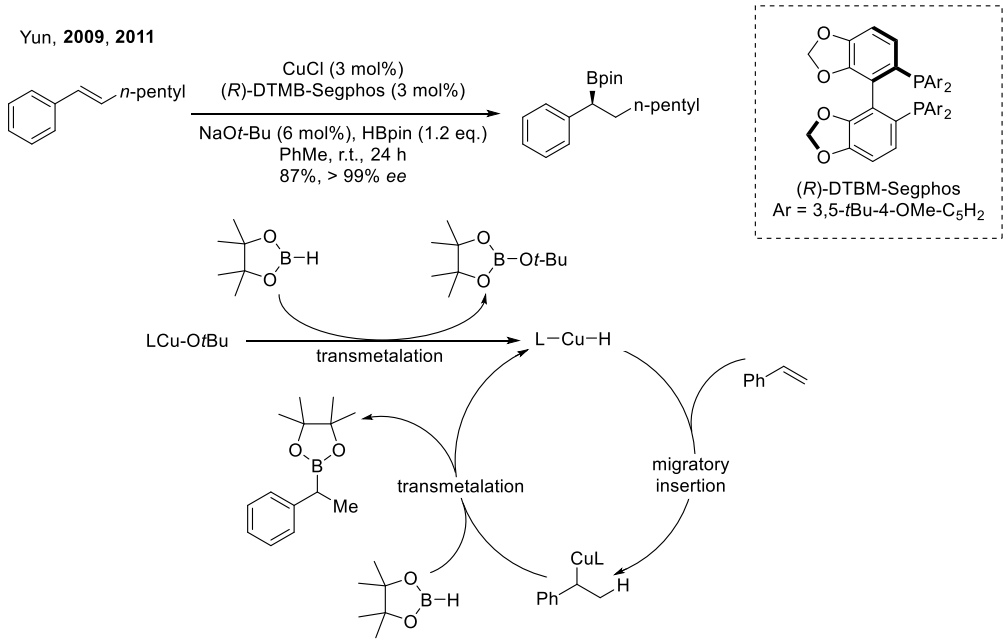
In 2003, Gevorgyan and co-workers reported the rhodium/phosphine-catalysed asymmetric hydroboration of cyclopropenes.[28] This methodology allowed access to enantiopure 2,2-disubstituted cyclopropyl boronic esters, in which either ester or alkoxy substituents were found to be essential for achieving high levels of enantioselectivity. Using β,γ-unsaturated amides as substrates, Takacs has developed a research program that allows access to β-boryl amides in excellent levels of regio- and stereocontrol.[29] In further important developments, the amide functionality was shown to direct regioselective asymmetric hydroboration of *E*- and *Z*-trisubstituted β,γ-unsaturated amides in a process that results in the introduction of two stereocentres with excellent level of diastereo- and enantiocontrol.[30,31] Using oxime functionalities to direct the hydroboration process, Takacs also developed important methodology for the synthesis of tertiary boronic esters, where expected anti-Markovnikov selectivity was overridden by the oxime directing group.[32] Tang and co-workers have also developed an amide-directed asymmetric hydroboration of α-arylenamides.[33] Under cationic rhodium(I) catalysis, in the presence of monodentate non-racemic phosphine ligands, these substrates can be hydroborated using bis(pinacolato)diboron (B_2pin_2) with exclusive Markovnikov selectivity generating valuable α-amino tertiary boronic esters in excellent levels of enantioselectivity.



Scheme 9: *Directed rhodium-catalysed alkene hydroborations.*

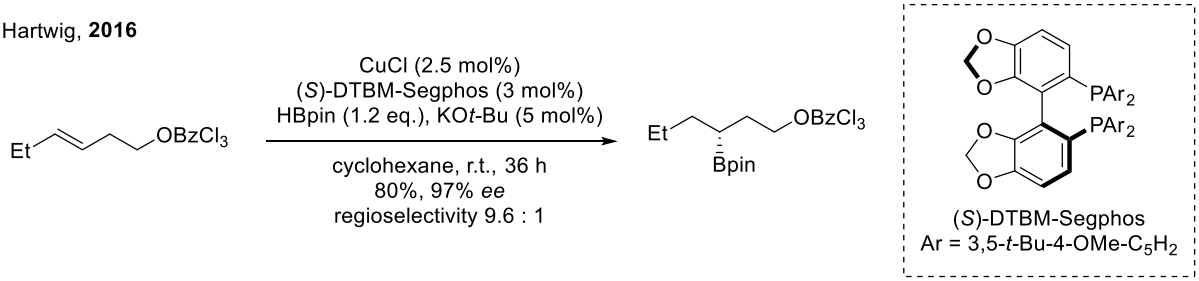
Although rhodium has dominated the field of direct metal-catalysed hydroboration of alkenes, copper has also been shown to facilitate this process, although the mechanism deviates from that proposed for rhodium, where the copper-catalysed process appears to be redox neutral. In 2009, Yun and co-workers reported the copper-catalysed hydroboration of styrenes using pinacolborane (PinBH).[34] The process is thought to start with a transmetalation of the copper(I)–alkoxy complex with PinBH, generating a copper–hydride species (Scheme 10). Insertion of the alkene into the Cu–H bond generates a copper–alkyl species, which is then proposed to undergo a transmetalation with PinBH, providing both the alkyl boronic ester and the catalytically active Cu–H species. Yun and co-workers were able to achieve the hydroboration of a range of terminal and 1,2-disubstituted styrenes in the presence of the P-chiral bis(phosphine) ligand, TangPhos; they later extended the method to Segphos-derived ligands, which exhibited exceptionally high levels of enantioinduction.[35] Although the method remains limited in scope

to styryl derivatives, this report presented an alternative manifold for metal-catalysed hydroboration reactions and described the first stereoselective transmetalation of a carbon(sp^3)–copper bond with pinacolborane.



Scheme 10: *Yun's copper-catalysed hydroboration of styrene derivatives.*

In 2016, Hartwig and co-workers reported an asymmetric copper/bis(phosphine)-catalysed hydroboration of alkenes (Scheme 11).[36] Following a mechanism similar to that proposed by Yun, the alkene inserts into the copper(I)–hydride species providing an alkyl–copper species, which then undergoes transmetalation with pinacolborane to provide the alkyl boronic ester. Hartwig's work, however, marks a major advance over previous copper-catalysed methods in that it achieves the enantioselective hydroboration of aliphatic internal alkenes, overcoming the limitation to styrene derivatives. In line with their previously reported hydroamination reactions of internal alkenes,[37] the high levels of regioselectivity reported in this work are thought to derive from the inductive effects of electronegative groups proximal to the alkene. Extensive DFT studies suggested that the proximal polar group helps to stabilise the negative charge that builds up during formation of the carbon–copper bond.



Scheme 11: *Hartwig's copper-catalysed regioselective hydroboration of internal alkenes.*

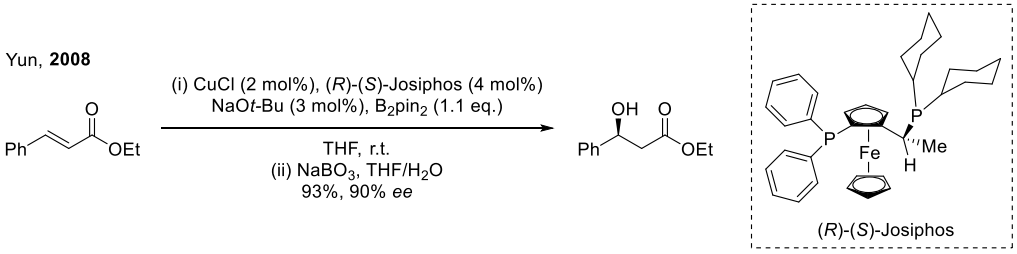
4. *Transition-Metal-Catalysed Borylation of Electron-Deficient Alkenes*

Hydroboration, as discussed in the previous section, involves the insertion of an alkene into a metal–hydride bond, followed by carbon–boron bond formation from the resultant alkyl–metal species (either by reductive elimination or transmetalation). For some classes of alkene, however, an alternative mechanism is possible leading to formal hydroboration products but by a markedly different mechanism.

In the non-catalysed hydroboration reactions described in Section 2 (*Non-Metal-Catalysed Hydroboration of Alkenes*), reactivity (and regioselectivity) was determined by the electrophilic nature of the boron moiety. In Section 3 (*Transition Metal-Catalysed Hydroboration of Alkenes*), the boron moiety was introduced through either reductive elimination or transmetalation of a metal–alkyl bond. Testament to the immensely varied reactivity of boron, an alternative pathway exists involving the insertion of the alkene into a metal–boron bond, a process that marks the boron moiety as nucleophilic. The metal–carbon bond then undergoes formal protodemetalation through a variety of pathways. The insertion of the alkene into a metal–boron bond, followed by transformation of the resultant metal–alkyl bond into a species other than a proton will be covered in further depth in Sections 8 (*Transition Metal-Catalysed Diboration*) and 9 (*Transition Metal-Catalysed Borylative Difunctionalizations of Alkenes*).

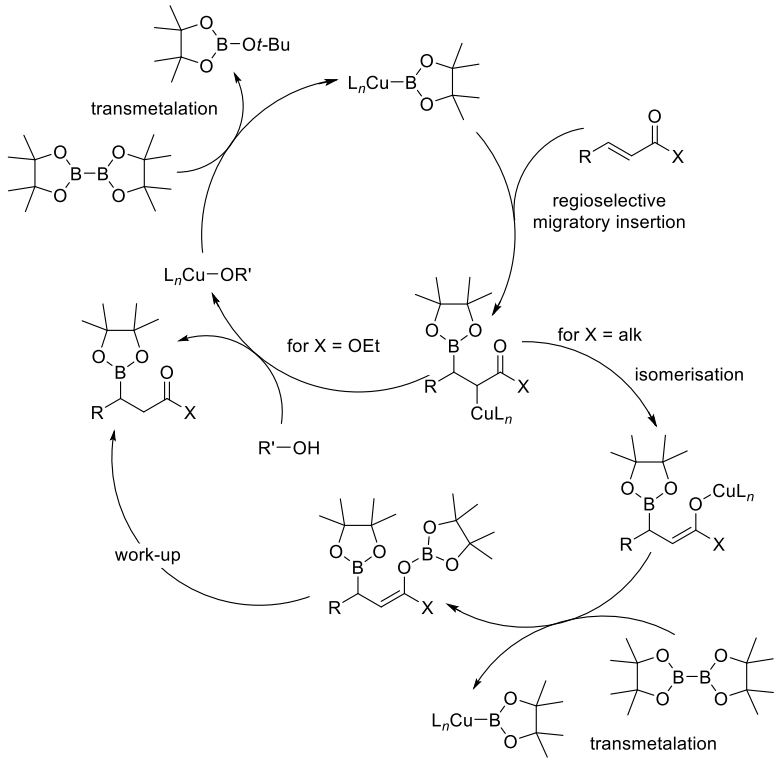
A number of metals have been used to catalyse the introduction of a boron moiety at the β-position of α,β-unsaturated systems.[38,39,40] An asymmetric variant of this process, however, was not reported until

2008, when Yun and co-workers described the copper/bis(phosphine)-catalysed asymmetric β-borylation of acyclic α,β-unsaturated esters and nitriles using B_2pin_2 (Scheme 12).[41]



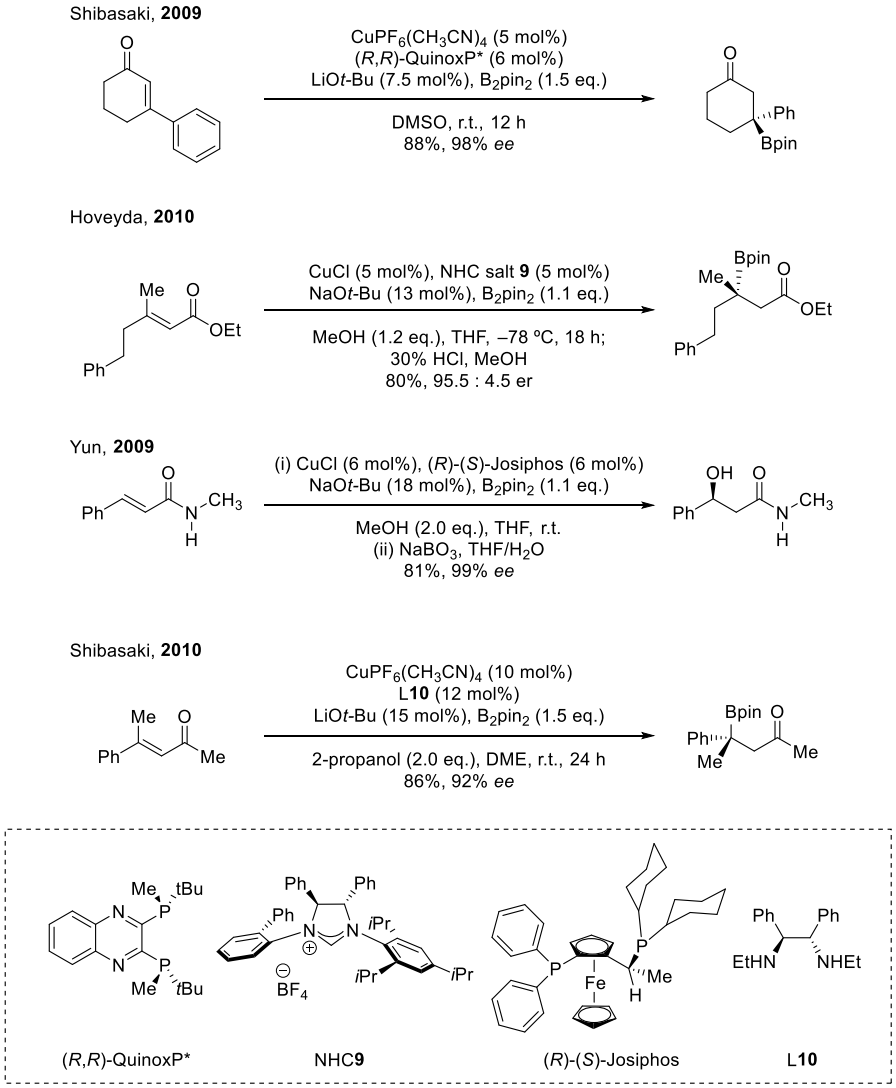
Scheme 12: *Yun's enantioselective protoboration of α,β-unsaturated esters.*

Considerable mechanistic studies have been undertaken with respect to non-stereoselective variants, particularly by Marder and co-workers.[42] These studies allow for rationalization of the observed regioselectivities, an appreciation of the dependence of mechanism on substrate class and insight into the origins of the efficacy of certain additives such as alcohols, which are often found to be essential for efficient reactivity. The active species in these processes is the ligated copper(I)–boryl complex, generated from the metathesis of the ligated copper(I)–X species (where X is often an alkoxide moiety) with the diboron reagent (Scheme 13). The alkene then inserts into the copper–boron bond, where regioselectivity is dictated by the nucleophilic attack of the Cu–B σ-bond on the more electrophilic β-position, thereby placing the resultant copper–carbon bond α to the carbonyl. Depending on the nature of the carbonyl group, this alkyl–copper species will either undergo direct protonolysis to provide the β-borylated product, or proceed by an isomerisation to the O-bound copper enolate, which can then undergo transmetalation with the diboron reagent to regenerate the active Cu species and provide the 1,4-diborylated product, which upon work-up collapses to the observed β-borylated product. Whether the mechanism proceeds through direct protonolysis of the copper–alkyl species or via the O-bound copper enolate, this protoboration process has since been used extensively for the β-borylation of α,β-unsaturated substrates.



Scheme 13: *Mechanistic rational for β-borylation of Michael acceptors.*

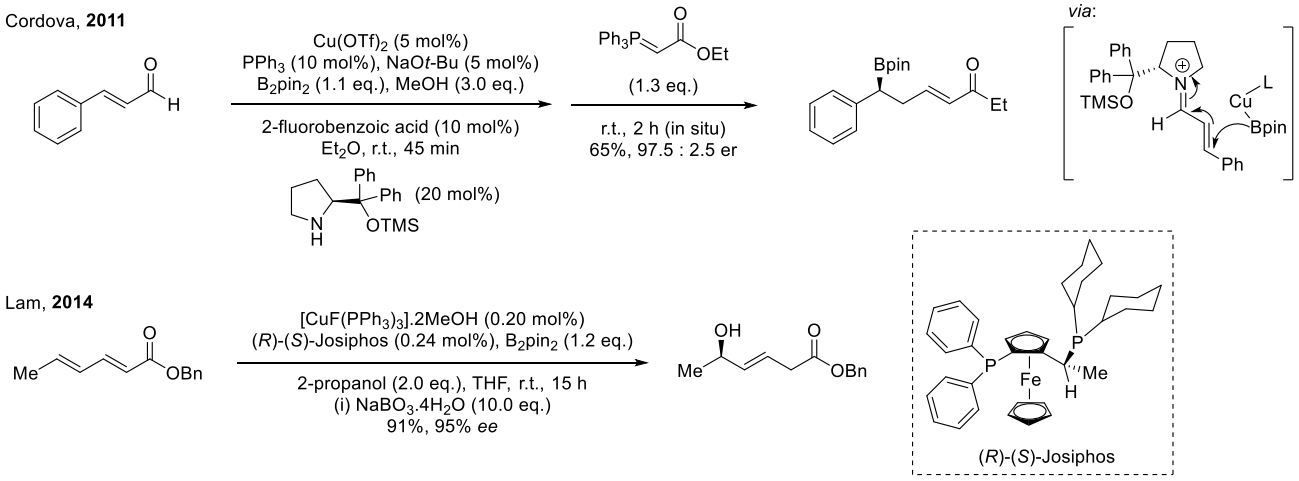
The copper/bis(phosphine)-catalysed β-borylation was extended to less reactive α,β-unsaturated amides with good levels of enantioselectivity for mono-β-substituted unsaturated systems.[43] Further important advances include the β-borylation of β,β-disubstituted substrates, which possess both lower reactivity and are less amenable to asymmetric induction owing to the similar steric size of the two β–substituents. Despite these issues, asymmetric β-borylations have been developed for both cyclic and linear systems.[44,45] Furthermore, selective β-borylations are also not limited to being effected by catalytic systems involving phosphine ligands and NHC ligands;[46,47,48,49] P,N ligands,[50] diamines,[45] and bipyridines[51] have all been shown, in combination with copper(I) salts, to be effective in the asymmetric β-borylation of α,β-unsaturated systems.



Scheme 14: *Copper-catalysed enantioselective β-borylations.*

Fernández and Whiting have reported the diphosphine/copper-catalysed β-borylation of α,β-unsaturated aldimines. This process not only provides access to valuable optically pure 1,3-aminoalcohols (upon reduction of the imine moiety), but also β-borylated aldehydes (by hydrolysis of the imine moiety), products that are difficult to access directly owing to competing 1,2-diboration.[52] Ibrahem and Córdova were also able to facilitate the β-borylation of unsaturated aldehydes, but through transient iminium formation; combining B_2pin_2 with an achiral phosphine ligand in the presence of catalytic amounts of chiral amine and $Cu(OTf)_2$, followed by trapping of the resultant β-borylated aldehydes in a Wittig process gave access to the formal 1,6-addition products with excellent level of

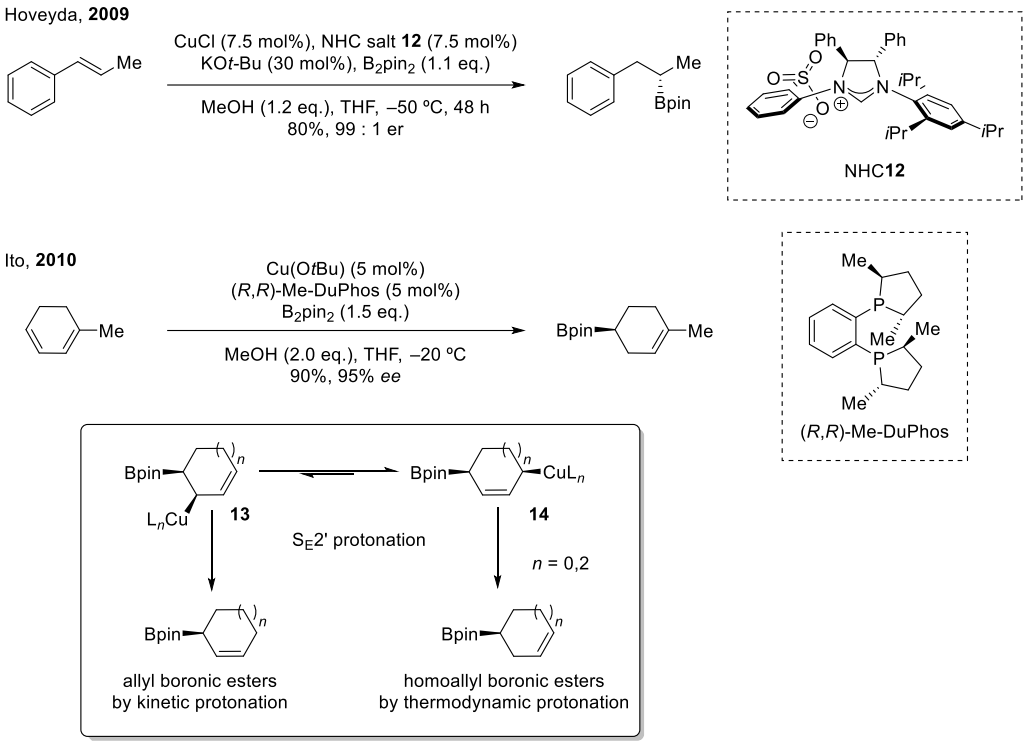
enantioselectivity (Scheme 15).[53] Iminium activation lowers the LUMO of the enal, favouring 1,4- over 1,2-borylation. Notably, asymmetry is not induced by chirality on copper, but by the transiently formed iminium. While Ibrahem and Córdova could access formal 1,6-addition homoallylic products, which are difficult to access owing to competing 1,4-addition, Lam and co-workers were able to carry out such a transformation directly (Scheme 15).[54] Using chiral diphosphine Josiphos in combination with a copper(I) salt they observed excellent levels of regioselectivity (>19:1 ratio of 1,6:1,4-addition) and enantioselectivity, provided the steric bulk at the δ position was limited (α-branching in the substituent at the δ position led to 1,4-addition products). This complementary process provides access to enantioenriched allylic boronic esters. A number of groups have also reported the trapping of the copper enolate that results from the copper-catalysed 1,4-borylation with aldehydes and ketones in both inter- and intramolecular aldol-type processes.[44,55]



Scheme 15: *Copper-catalysed borylation of enals and dienones.*

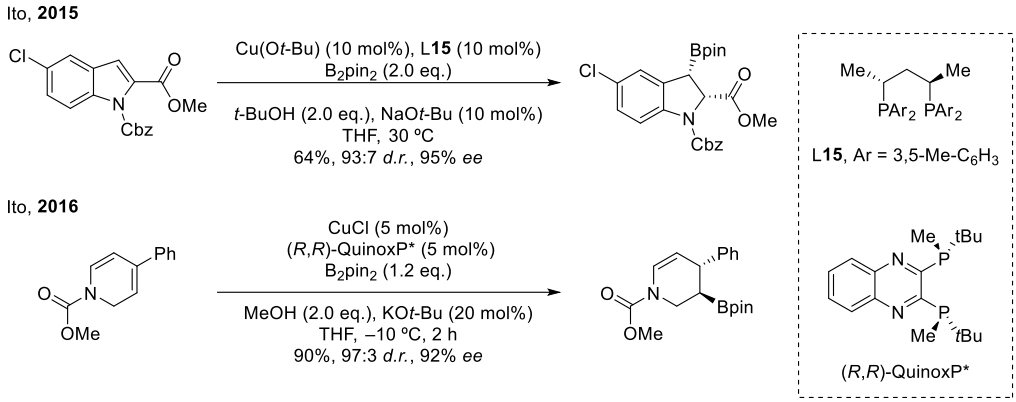
Although the mechanistic protocol of inserting the alkene into the copper–boron bond, followed by derivatisation of the resultant Cu–alkyl bond by protonolysis, has been most commonly applied to α,β-unsaturated systems, a number of other classes of alkene have been reported to undergo borylation by a mechanism of this type. In 2009, Hoveyda and co-workers reported the enantioselective copper-catalysed protoboration of aryl-substituted alkenes (with no further activation from a conjugated carbonyl moiety)[56]. A bidentate chiral imidazolium salt in the presence of a strong base and a copper(I)

salt was used to effect the asymmetric protoboration of a variety of styryl derivative (Scheme 16). Perhaps most importantly, the regioselectivity of the reaction was opposite to that observed for the transition metal-catalysed hydroboration reactions using PinBH (see Section 3, *Transition Metal-Catalysed Hydroboration of Alkenes*), installing the Bpin moiety at the position β to the aryl group. As for many of the borylation reactions of electron-deficient alkenes described above, methanol was found to be essential for good reactivity, presumably required to protonate the transient alkyl–copper bond. 1,3-Dienes have also been shown to be susceptible to asymmetric protoboration under copper catalysis; Ito and co-workers reported the asymmetric copper(I)-catalysed borylation of 1,3-dienes to provide enantioenriched homoallyl- or allyl boronic esters (Scheme 16).[57] Interestingly, for some ring sizes, temperature appears to play an important role in whether 1,2- or 1,4-protoboration occurs. At lower temperatures, the allyl boronic esters dominate, a selectivity explained by the authors as being due to S_E2' protonation of the kinetic insertion intermediate **13**. Conversely, higher temperature would allow **13** to equilibrate to the thermodynamically more stable **14**, which upon S_E2' protonation provides the homoallyl boronic ester products. Although cyclic 1,3-dienes can be protoborated with excellent levels of asymmetric induction, the corresponding acyclic 1,3-dienes provide the corresponding boronic esters with poor enantioselectivity. Tortosa and co-workers have also reported the asymmetric protoboration of both cyclopropenes and cyclobutenes with B_2pin_2 under copper/bis(phosphine) catalysis.[58,59]



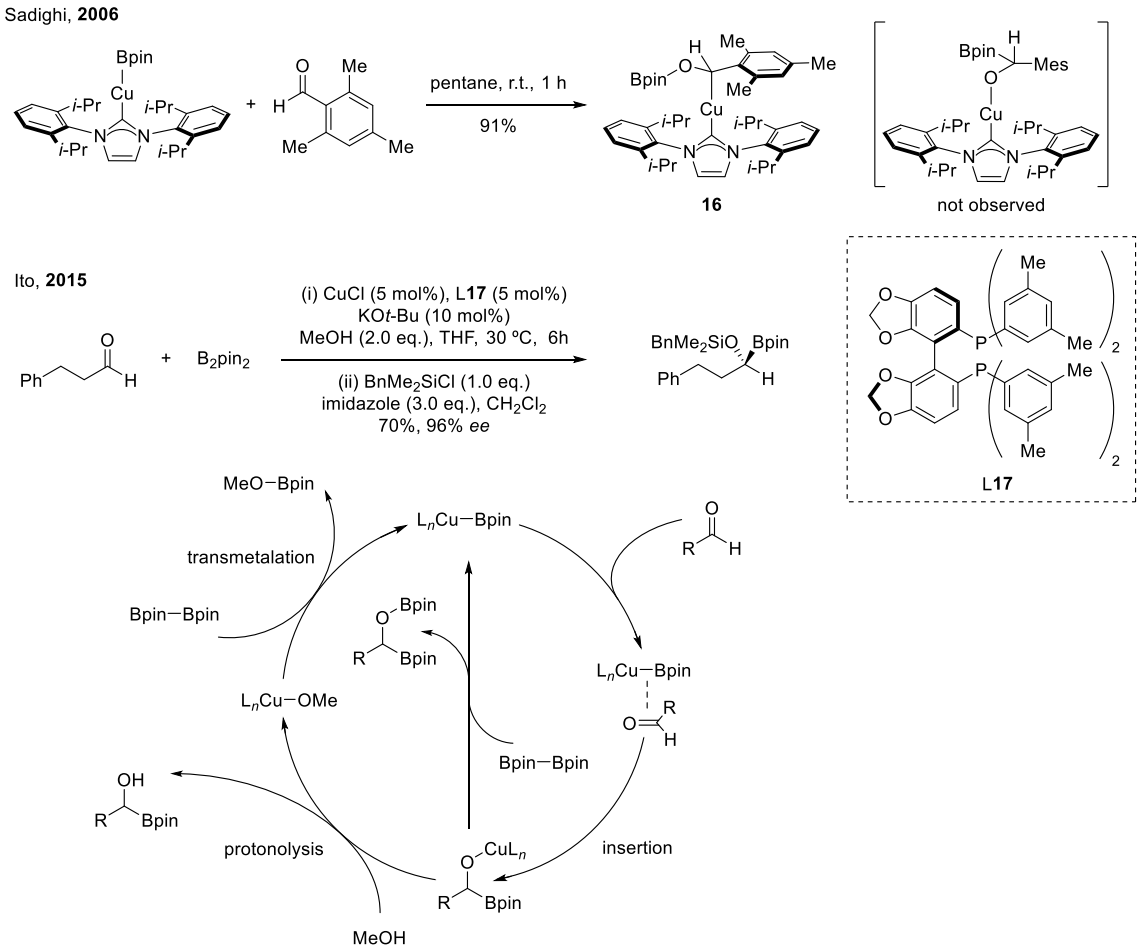
Scheme 16: *Copper-catalysed enantioselective protoboration of unactivated substrates.*

In an interesting development in copper-catalysed asymmetric protoboration reactions, Ito and co-workers have recently reported a number of studies into the copper-catalysed enantioselective borylative functionalization of heterocycles. Using electron-deficient indoles, Ito and co-workers were able to carry out an enantioselective borylative dearomatization with B_2pin_2, providing chiral 3-borylindoline products with excellent levels of asymmetric induction (Scheme 17).[60] In a later study they described the asymmetric synthesis of chiral piperidines by a two-step procedure: readily available pyridines were subjected first to dearomative reduction, followed by enantioselective copper-catalysed protoboration of the resulting 1,2-dihydropyridines.[61] Again, excellent levels of asymmetry were obtained providing highly complex alkyl boronic esters. This two-step process was also found to be amenable to the synthesis of enantioenriched tetrahydroquinolines.[62]



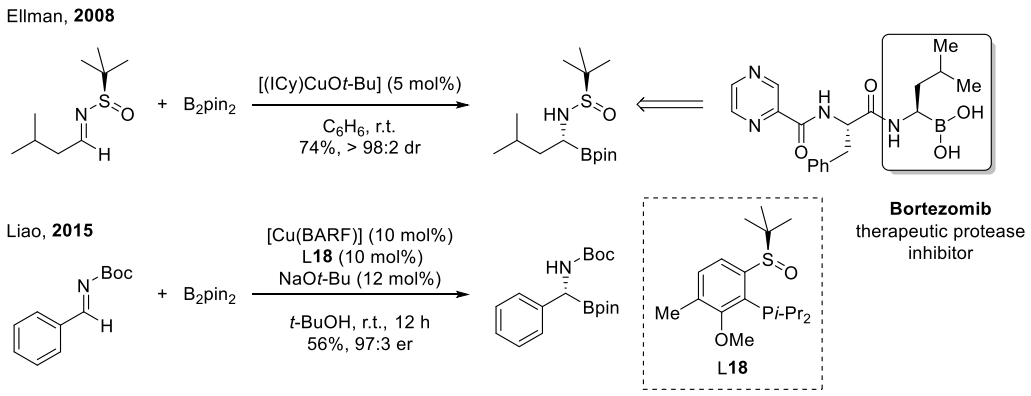
Scheme 17: *Copper-catalysed enantioselective borylation of heterocycles.*

This protoboration reactivity platform has also been used for the borylation of unsaturated carbon–heteroatom bonds. In pioneering studies by Sadighi and co-workers in 2006, aliphatic and aromatic aldehydes were shown to react with (NHC)Cu(boryl) complexes to generate species **16**, containing a copper–carbon σ bond (Scheme 18).[63] The alternative insertion regioisomer containing the [Cu–O–C–B] linkage was not observed. Species **16** was shown to be a competent catalyst for the diboration of aldehydes in the presence of B_2pin_2. Marder and Lin later established, through extensive DFT calculations, that the reaction proceeds through insertion of the aldehyde into the copper–boryl bond to give the [Cu–O–C–B] species, followed by transmetalation of the copper–oxygen species with B_2pin_2 providing the diboration product and regenerating the catalytically active copper–boryl species.[64] Sadighi's result can be explained in terms of an isomerisation to the thermodynamically preferred [B–O–C–Cu] in the absence of B_2pin_2 to facilitate transmetalation. Molander later optimized the Sadighi borylation with the introduction of a protic additive to facilitate protolytic catalyst turnover, reducing the reaction time considerably.[65] Ito and co-workers have recently rendered the process asymmetric through the introduction of chiral diphosphine ligands.[66] Following silyl protection, the α-alkoxy boronic esters can be obtained in good yield and excellent enantioenrichment.



Scheme 18: *Copper-catalysed enantioselective borylation of aldehydes.*

Imines have also been shown to undergo copper-catalysed borylation, generating α-amino boronic esters, a class of compounds that shows valuable anti-cancer properties. In 2008, Ellman and co-workers pioneered the use of chiral *N*-*tert*-butanesulfinyl imines in a highly diastereoselective borylation of the unsaturated carbon–nitrogen bond with B_2pin_2.[67] Using Sadighi's catalyst, α-amino boronic esters were obtained in excellent yields and levels of diastereoselectivity (Scheme 19). The authors also used this method in an efficient synthesis of bortezomib, a protease inhibitor drug used for the treatment of multiple myeloma and mantel cell lymphoma. They, and others, were later able to develop an improved catalytic system by using more oxygen- and moisture-stable copper catalysts.[68,69] Li co-workers used optically pure *N*-phosphinylimines in a related strategy for the synthesis bortezomib.[70] Using chiral ligands on copper, the groups of Lin[71] and Liao[72] have independently reported the asymmetric copper-catalysed borylation of *N*-benzoyl and *N*-Boc aldimines in moderate to good levels of enantioselectivity.

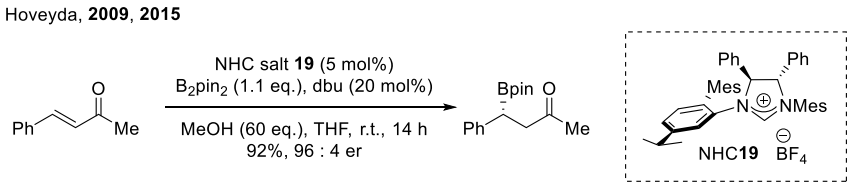


Scheme 19: *Copper-catalysed enantioselective borylation of imines.*

5. *Transition-Metal-Free Borylation of Electron-Deficient Alkenes*

An important report from Hoveyda and co-workers in 2009 detailed the β-borylation of α,β-unsaturated ketones in the absence of a metal catalyst.[73,74] In the presence of catalytic quantities of an N-heterocyclic carbene (NHC), B_2pin_2 was found to undergo 1,4-addition to the unsaturated systems in excellent yield and regioselectivity providing both cyclic and acyclic secondary and tertiary alkyl boronic esters. The underlying principle of the process is that the association of the NHC with the diboron reagent activates it towards attack of the electrophilic α,β-unsaturated ketone. Such a proposal was supported by DFT calculations which showed a lengthening and polarization of the B–B bond upon association of the NHC, where the electron density is strongly polarized towards the non-associated boron atom. These calculations were further supported by NMR studies, which indicated the disappearance of the ^{11}B NMR signal for B_2pin_2 within five minutes of treatment with NHC **19** at room temperature; two different signals were observed, both significantly shifted upfield. This hypothesis was later validated by a report from Marder and co-workers, who provided X-ray crystallographic studies of an NHC–diboron complex.[75] While this initial report provided racemic β-borylated products, Hoveyda later reported the asymmetric variant using chiral imidazolium salts in combination with an organic base (Scheme 20).[76] Excellent yields and levels of enantioselectivity could be achieved for the β-borylation of a wide variety of substrates, including α,β-unsaturated ketones, esters, amides and aldehydes; a later report extended

the methodology to β,β-disubstituted enones, providing access to optically pure tertiary alkyl boronic esters.[77]



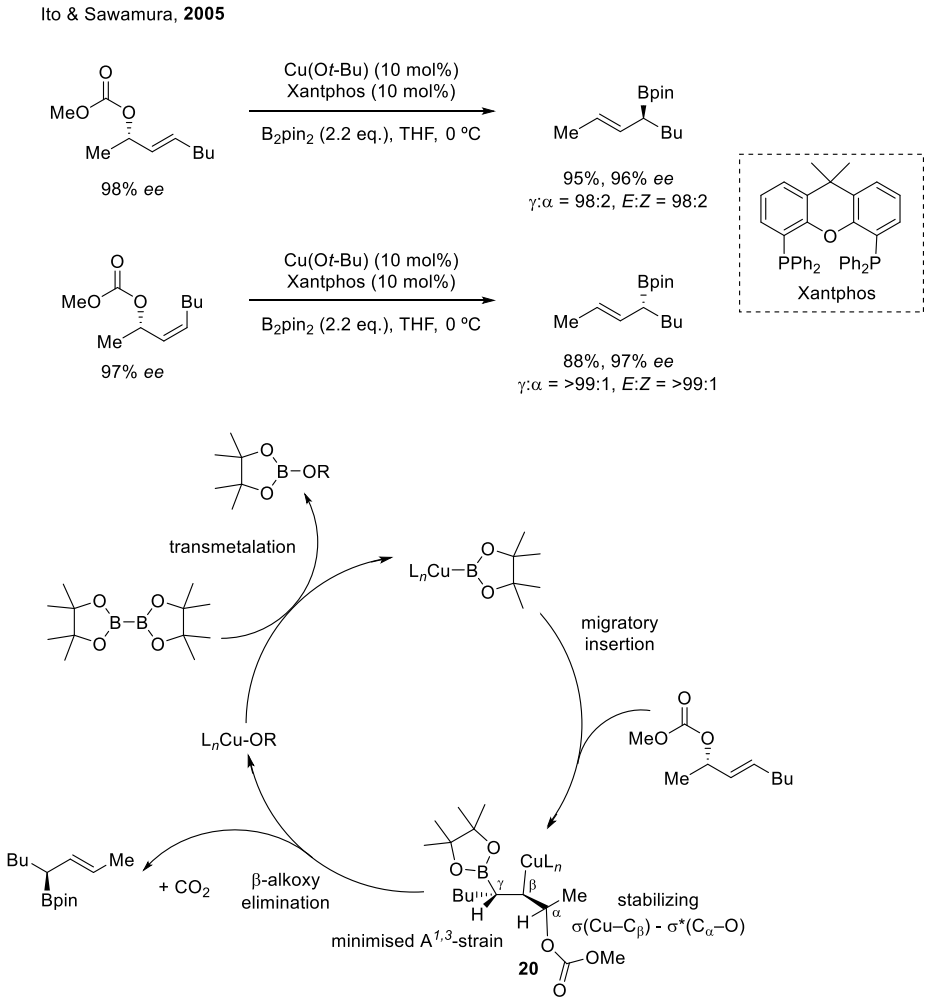
Scheme 20: *Hoveyda's metal-free asymmetric borylation of α,β-unsaturated ketones.*

Fernández and co-workers have also reported the asymmetric β-borylation of α,β-unsaturated compounds and tosylaldimines in the absence of metal catalysts.[78,79] Using chiral diphosphines to activate the B–B bond of B_2pin_2 towards nucleophilic attack of the unsaturated system, the authors reported good conversions and moderate levels of enantioselectivity for the synthesis of secondary- and α-amino boronic esters.

6. *Asymmetric Borylation of Allylic Electrophiles*

In 2005, Ito and Sawamura developed a γ-selective stereospecific substitution reaction of allylic carbonates with B_2pin_2.[80] Using a copper(I)/Xantphos catalyst system, they transformed allylic carbonates into the corresponding chiral allylboron species with excellent levels of α-to-γ chirality transfer (Scheme 21). As for the processes described in Section 4 (*Transition Metal-Catalysed Borylation of Electron Deficient Alkenes*), the reaction is proposed to start with the formation of a boryl–copper(I) species, formed from the reaction of a copper(I)–alkoxy species with B_2pin_2. Insertion of the alkene into the Cu–B bond installs the boryl group and generates a copper(I)–alkyl species **20** on the adjacent carbon atom. Subsequent β-alkoxy elimination from copper–alkyl species **20** releases the allyl boronic ester and a copper–carbonate species, which can then undergo decarboxylation, regenerating the catalytically active copper–alkoxy species. The regioselectivity of the alkene insertion into the Cu–B bond occurs with high selectivity, positioning the Cu–alkyl bond β to the carbonate moiety owing to stabilising interactions with the adjacent C–O bond. The stereospecificity of the process was confirmed

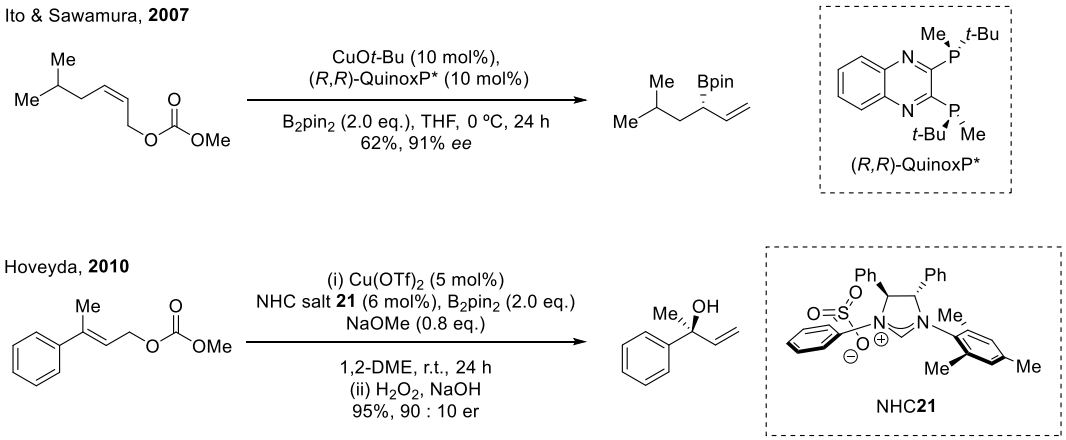
by the reaction of both *E* and *Z* isomers: the two isomers provided the opposite antipodes of the allyl boronic ester product, thus supporting a mechanism in which the allyl carbonate adopts a conformation minimising allylic 1,3-strain followed by *anti*-attack by the copper–boryl species.



Scheme 21: *Copper-catalysed stereospecific borylation of chiral allylic carbonates.*

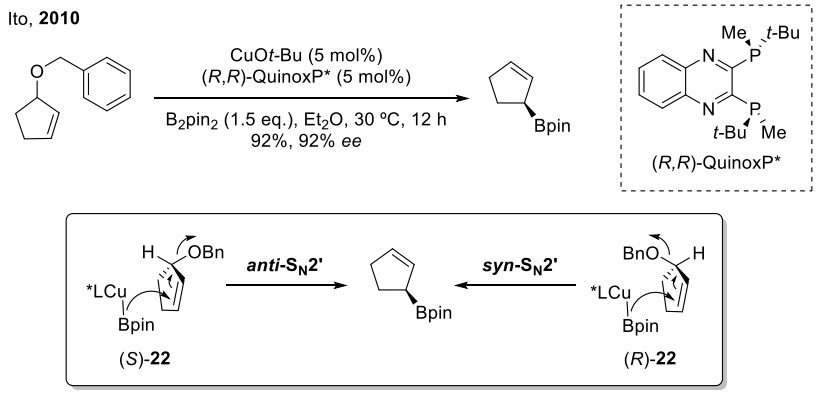
In 2007, Ito and Sawamura developed a copper-catalysed enantioselective substitution of *Z*-allylic carbonates with B_2pin_2[81]. Using the chiral bis(phosphine) QuinoxP* ligand they could access α-chiral allyl boronic esters with excellent levels of enantioselectivity (Scheme 22). Again, the regioselectivity is thought to arise through stabilisation of transient β-Cu–alkyl species by the adjacent C–O bond. Interestingly, the procedure leads to much poorer levels of enantioselectivity when the *E*-allylic carbonates are used. Ito later extended this process to the γ substitution of allyl acetals, providing access

to α-chiral γ-alkoxyallyl boronic esters.[82] In 2010, Hoveyda and co-workers reported an NHC–copper-catalysed borylation of allylic carbonates.[83] Importantly, this process provided the allyl boronic esters with excellent *ee* values when either the *E*- or *Z* carbonates were used (providing the allyl boronic esters with opposite absolute stereochemistry). Furthermore, by using γ,γ-disubstituted allylic carbonates, the authors could access tertiary allyl boronic esters with high levels of enantioselectivity.



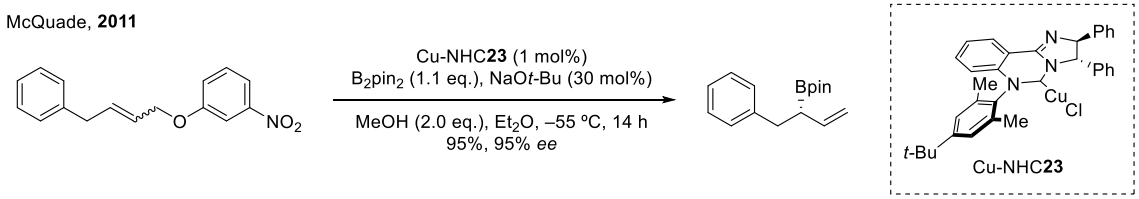
Scheme 22: *Copper-catalysed enantioselective borylation of allylic carbonates.*

In an important mechanistic development, Ito and Sawamura reported the transformation of racemic allylic ethers into highly enantioenriched allyl boronic esters.[84] Methods for the transformation of chiral racemic substrates into enantioenriched products are highly desirable. Deracemization processes such as dynamic kinetic resolution (DKR) and dynamic kinetic asymmetric transformation (DYKAT) are most common. Ito and Sawamura's report, however, describes a mechanistically distinct approach in which the two enantiomers of the allylic ether substrate react by different pathways, leading to the same enantiomer of the allyl boronic ester (Scheme 23). As before, regioselective insertion of the alkene into the Cu–B bond positions the boryl moiety in the γ position. Subsequent collapse of the β-copper–alkyl species and expulsion of the alkoxide provides the allyl boronic ester. The asymmetric induction is thus determined by which face of the allylic ether **22** the copper(I)–boryl species approaches; for enantiomer (*S*)-**22** an *anti*-S_N2' pathway occurs, while for the opposite enantiomer (*R*)-**22** the corresponding *syn*-S_N2' pathway occurs, thereby generating the same enantiomer of product.



Scheme 23: *Ito's copper-catalysed enantioconvergent synthesis of chiral allyl boronic esters.*

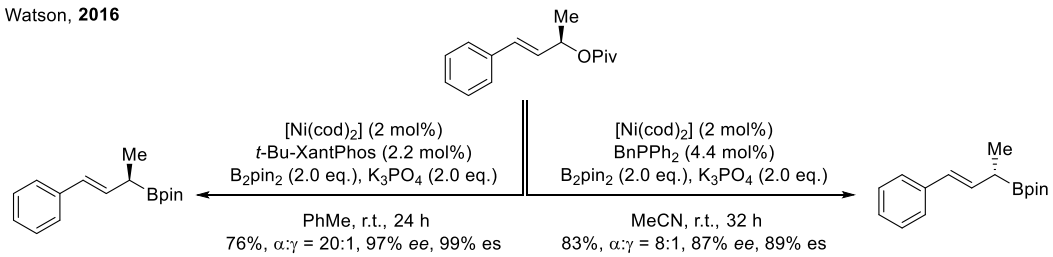
McQuade and co-workers have described a stereoconvergent process for accessing α-chiral allylic boronic esters, in which both the *E*- and *Z* isomers of allylic ethers undergo substitution to give the same enantiomer of product (Scheme 24).[85] Using an NHC–copper(I) catalyst system, the authors postulate that the reaction does not proceed by initial isomerization of the alkene and subsequent transformation of a common intermediate (no isomerization was observed when the reaction was monitored by ^{1}H NMR), but rather that the catalyst reacts with the face of each isomer that is required for generating the same enantiomer of product.



Scheme 24: *Copper-catalysed enantioselective stereoconvergent synthesis of chiral allyl boronic esters*

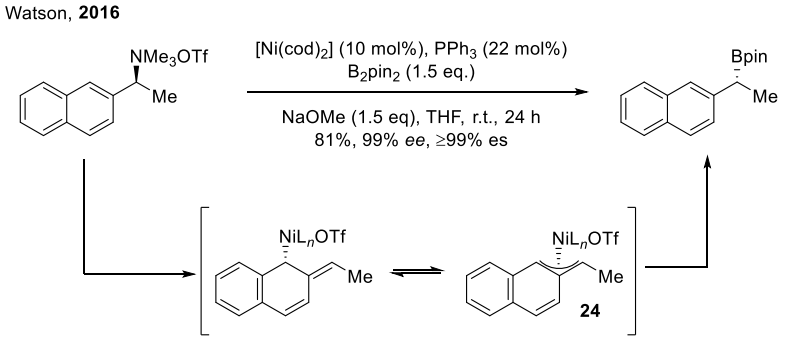
Watson and co-workers have recently shown that nickel catalysis can be used to effect the stereospecific borylation of γ-aryl allylic pivalates with B_2pin_2, providing α-stereogenic γ-aryl allylic boronic esters in high levels of enantioselectivity (Scheme 25).[86] Interestingly, the stereospecificity of the substitution could be inverted through a change in solvent: in non-polar solvents, high levels of stereoretention is observed, while in polar solvents, such as acetonitrile, the allylic boronic esters are obtained with stereoinversion. The authors propose a mechanism involving a π-allyl nickel intermediate, which undergoes regioselective and stereoretentive reductive elimination. In non-polar solvents, the oxidative

addition generating the key π-allyl nickel intermediate is directed by the pivalate group via a 7-membered transition state, leading to retention. In polar solvents, such as acetonitrile, this directing interaction is inhibited and oxidative addition occurs through an open transition state leading to stereoinversion.



Scheme 25: *Watson's nickel-catalysed stereospecific borylation of allylic pivalates.*

Although not an allylic substitution, similar mechanistic arguments can be used to understand Watson's nickel-catalysed stereoinvertive borylation of benzylic ammonium salts.[87] Good levels of stereospecificity could be obtained for the nickel-catalysed cross-coupling of benzylic ammonium triflates with B_2pin_2, providing enantioenriched benzylic boronic esters (Scheme 26). The authors propose that oxidative addition occurs by *anti* S_N2' attack of the nickel complex at the *ortho* position and generation of π-allyl species **24**. Regioselective retentive reductive elimination then provides the observed stereoinverted benzylic boronic ester products.



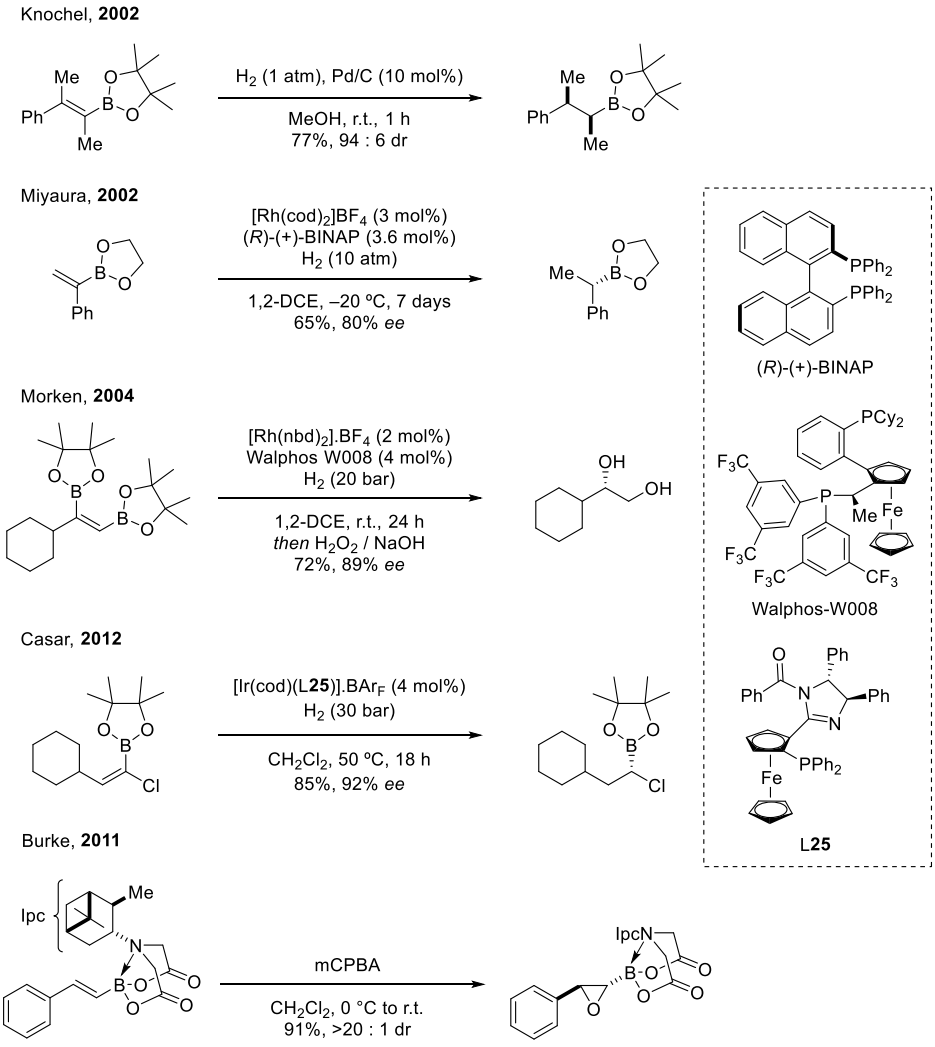
Scheme 26: *Nickel-catalysed stereoinvertive borylation of benzylic ammonium salts.*

7. *Asymmetric Transformation of Prochiral Boron-Containing Substrates*

In the methods described above, the π system of an organic substrate reacts with a boron containing reagent and, through a variety of mechanisms, the boryl moiety is introduced. There is, however, an alternative method for the synthesis of a stereodefined alkyl boronic ester: the asymmetric transformation of a prochiral boronic ester. Such processes often overcome the issues associated with regioselectivity encountered with hydroboration methods and provide access to products unattainable by the methods discussed previously.

Knochel and co-workers first probed the possibility of accessing secondary alkyl boronic esters by the hydrogenation of the corresponding vinylboronic esters in 2002.[88] While not asymmetric, excellent levels of diastereoselectivity could be achieved, allowing control of two adjacent stereocentres (Scheme 27). In 2002, Miyaura and co-workers disclosed the first asymmetric hydrogenation of vinyl boronic esters.[89] Using a rhodium/chiral diphosphine catalyst system under an atmosphere of dihydrogen, 1-phenylethenylboronic esters could be transformed into the corresponding benzylic boronic esters. While the reaction was limited to a single substrate and *ee* values of up to only 80% could be achieved, it has since been developed into a valuable method for the synthesis of stereodefined alkyl boronic esters.[90] Morken later developed a method with improved enantioselectivity for the hydrogenation of vinyl bis(boronic esters).[91] Using a cationic rhodium catalyst and the phosphine ligand, Walphos, good to excellent levels of asymmetric induction could be obtained for a much wider substrate scope, providing the chiral diols after oxidation. Under very similar reaction conditions, Morken would later show that simple vinyl boronic esters could also undergo asymmetric hydrogenation providing the secondary boronic esters with excellent levels of stereocontrol.[92] Further studies followed using iridium/chiral P,N ligands.[93,94] An interesting extension of this method was reported by Časar and co-workers: using 1-halo-1-alkenyl boronic esters as substrates, α-haloalkyl boronic esters could be accessed using an iridium/P,N ligand system in excellent levels of enantioselectivity, provided the β position was sufficiently bulky (aryl or branching in this position).[95,96,97] The products from this process are of considerable synthetic utility, where methods for the substitution of the halo moiety by Matteson-type homologation reactions provides the opportunity to access a wide variety of stereodefined

secondary alkyl boronic esters (Section 11: *1,2-Metallate Rearrangements of Boronate Complexes*). Direct stereospecific transformation of the halo group into an amine further provides valuable α-amino boronic acids. Conversely, Burke and co-workers have reported a highly diastereoselective oxidation of vinylboronic esters appended with a pinene-derived iminodiacetic acid ligand (Scheme 27).[98] The oxiranyl boronic esters formed in this process can be readily transformed via a 1,2-boryl migration into versatile products such as α-boryl aldehydes and β-haloboronic esters.

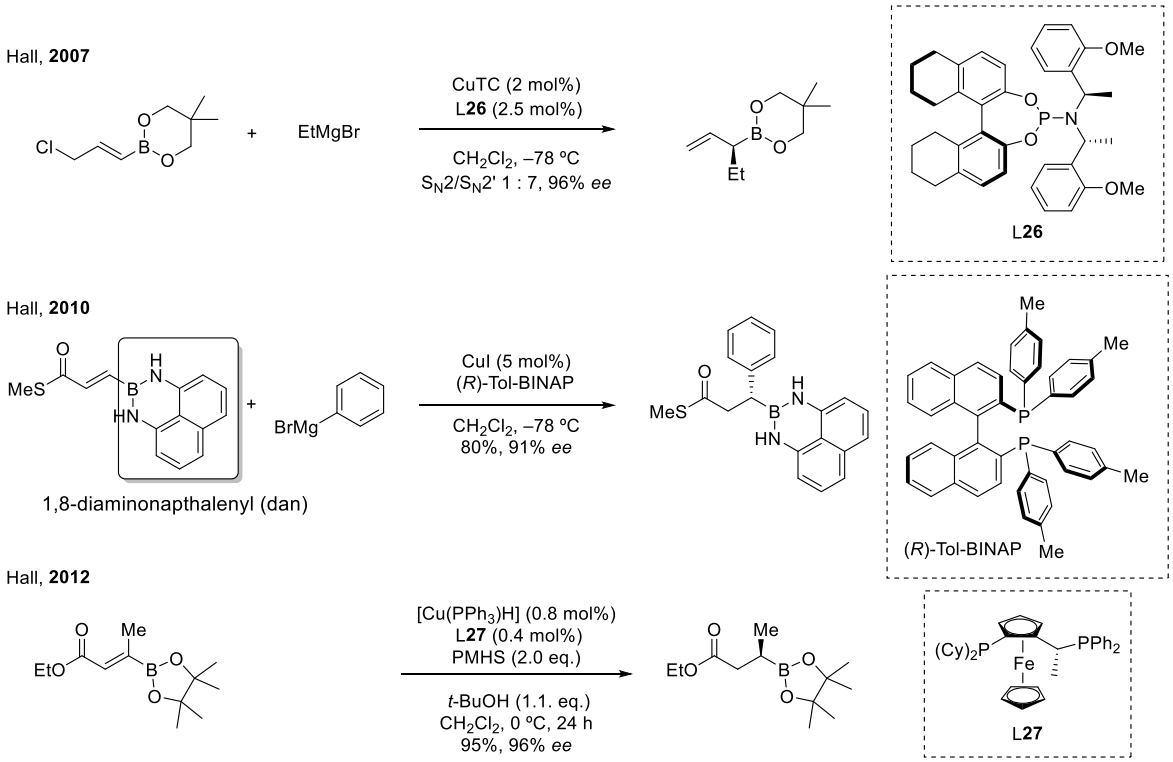


Scheme 27: *Stereoselective reduction and oxidation of vinylboronic esters.*

Since 2007, the Hall group has developed a variety of methods that also use prochiral boronic esters as substrates, providing structurally diverse secondary alkyl- and allyl boronic esters with excellent levels

of stereocontrol. In 2007, Hall and co-workers reported the asymmetric copper(I)-catalysed S_N2' addition of Grignard reagents to 3-halopropenyl boronic esters (Scheme 28).[99] Despite potential competing pathways involving S_N2 substitution or allylic Matteson homologation (which would provide the S_N2'-type product but presumably in racemic form), the authors were able to achieve good levels of chemoselectivity for S_N2' substitution and access the allyl boronic esters in excellent levels of enantioselectivity. In a conceptually similar process, Hall and co-workers attempted to access enantioenriched α-chiral allyl boronic esters by the iridium-catalysed asymmetric allylic alkylation of 1-propenyl boronic esters.[100] Although some useful levels of selectivity were achieved, the reaction was plagued by poor S_N2/S_N2' ratios.

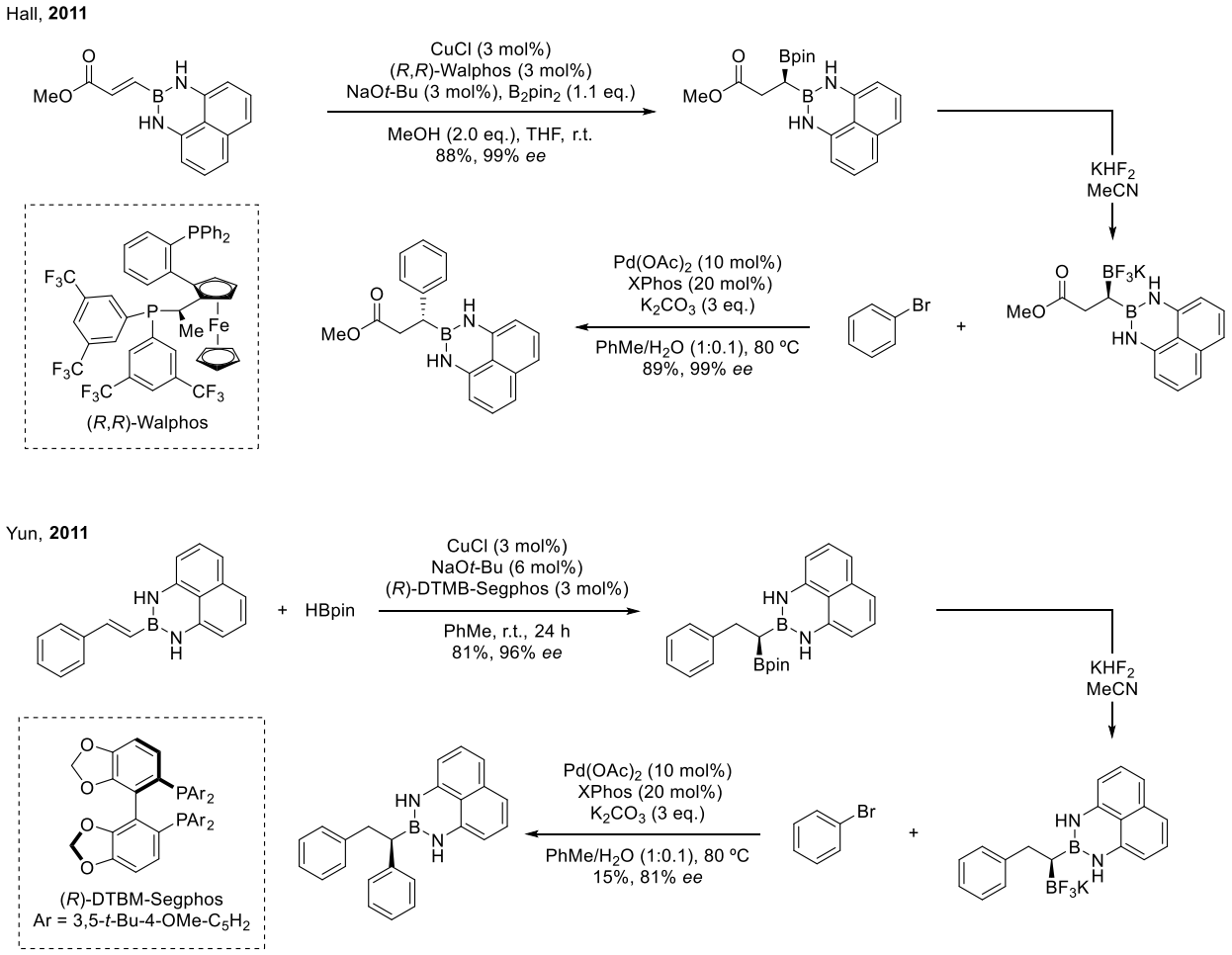
Hall and co-workers later described the catalytic enantioselective conjugate addition of Grignard reagents to 3-boronyl unsaturated esters and thioesters.[101] Not only could excellent levels of selectivity be achieved by using a copper(I) salt in combination with chiral diphosphine Tol-BINAP for the addition of alkyl Grignard reagents, the corresponding aryl reagents also underwent the addition with excellent stereocontrol. Both Hall[102,103] and Yun[104] have also reported the copper-catalysed reduction of β-boronyl-β-alkyl α,β-unsaturated esters to generate the corresponding secondary alkyl boronic esters with excellent levels of enantioselectivity when the β-substituent was a methyl group. An increase in steric bulk at this position led to diminished levels of enantioselectivity.



Scheme 28: *Hall's copper-catalysed S_N2' and conjugate additions.*

In an elegant development to their conjugate addition work, Hall and co-workers prepared enantioenriched 1,1-diboron compounds by the asymmetric copper(I)-catalysed conjugate addition of a Bpin moiety (from B_2pin_2) to 1,8-diaminonapthalenyl (dan) 3-boronyl enolates (Scheme 29).[105,106] Key to their strategy was the differentiation of the two boronic ester moieties at the β position, which they exploited through the subsequent selective Suzuki–Miyuara cross-coupling of the Bpin moiety (via transformation to the corresponding tetrafluoroborate salt), providing the benzylic boronic esters with compete enantiospecificity. Yun and co-workers later showed that the key chiral non-racemic geminal bis(boronic ester) motif could also be obtained through an enantioselective copper-catalysed hydroboration of vinylboronic esters.[107] Hydroboration of the vinyl-Bdan esters with PinBH under copper(I)/diphosphine catalysis provided the 1,1-diboron compounds in excellent levels of regio- and enantioselectivity. Analogously to Hall, Yun was able to selectively transform the Bpin moiety into an aryl group through palladium-catalysed cross-coupling. Interestingly, in the absence of the coordinating carbonyl group available to Hall, the cross-coupling reaction proceed in low yield and with some

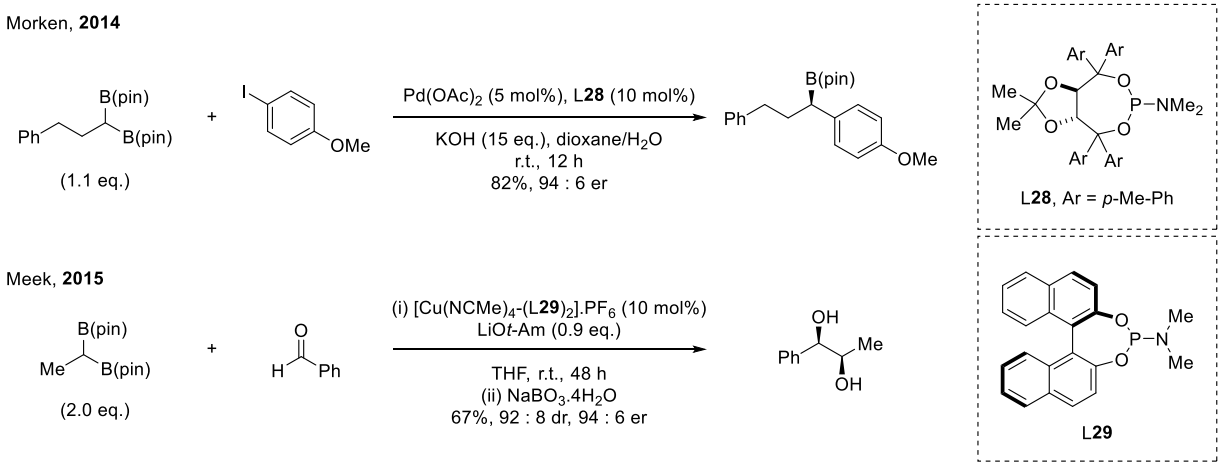
erosion of *ee* value. Furthermore, the cross-coupling was shown to proceed with stereochemical retention (as opposed to the stereochemical inversion observed by Hall and co-workers).



Scheme 29: *Synthesis of enantioenriched 1,1-diboron compounds.*

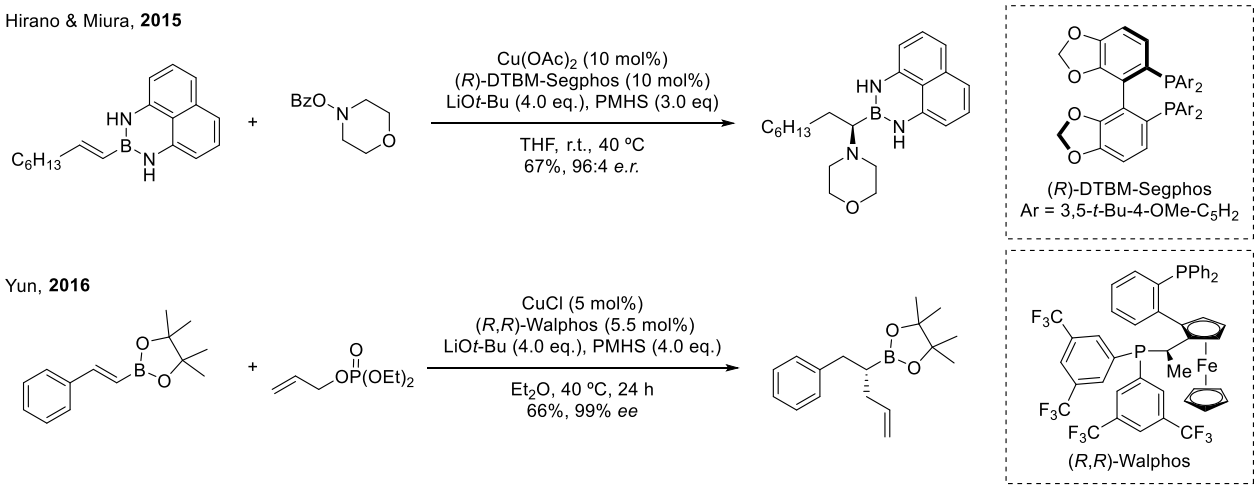
In the above studies, both Hall and Yun drew on the observation by Shibata and co-workers in 2010 that 1,1-diborylalkanes undergo selective Suzuki–Miyaura cross-coupling reactions under remarkably mild conditions (room temperature directly from the pinacol boronic ester).[108] Further harnessing this reactivity, Morken has developed a highly successful enantiotopic-group-selective cross-coupling of achiral geminal bis(pinacol boronic esters) with aryl halides.[109] Using a palladium/chiral phosphoramidite catalyst system the authors could convert symmetric geminal bis(pinacol boronic esters) into the corresponding alkyl boronic esters in excellent enantioselectivity (Scheme 30). Mechanistic studies suggest that the process proceeds through a stereochemistry-determining

transmetalation that occurs with inversion of stereochemistry, followed by a retentive reductive elimination. They later extended the methodology to allow the cross-coupling of vinyl halides providing access to valuable allylic boronic esters in high levels of stereoselectivity.[110] The key chiral α-boryl alkylmetal species utilised in the Morken methodology was also used in later work by Meek and co-workers for the copper-catalysed addition of 1,1-diboron reagents to aldehydes generating 1,2-hydroxy boronic esters in excellent levels of enantio- and diastereocontrol.[111] Using a monodentate phosphine–copper(I) complex in the presence of a lithium alkoxide base, 1,1-diboron reagents could undergo efficient stereoselective addition to a range of alkyl and aryl aldehydes.



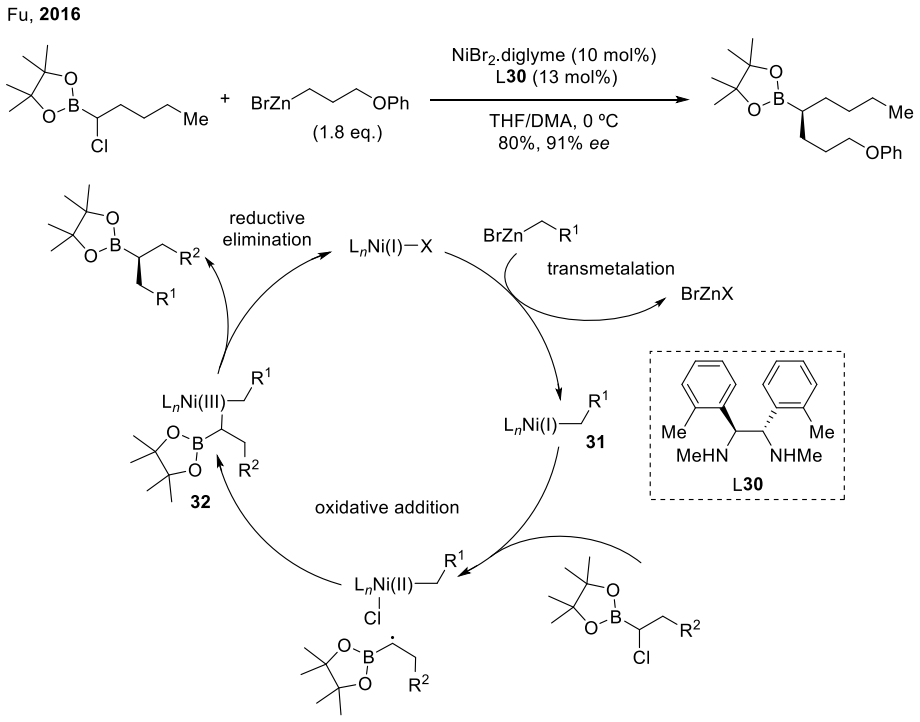
Scheme 30: *Enantiotopic-group-selective cross-coupling of achiral geminal bis(pinacol boronic esters).*

An alternative method for accessing chiral α-boryl alkylmetal species was realized by Hirano and Miura in their copper-catalysed enantioselective hydroamination of alkenyl boronic esters (Scheme 31).[112] An initial hydrocupration event generates a chiral α-boryl organocopper species, for which regioselectivity is controlled by hyperconjugation between σ(Cu–C) and the empty p orbital on boron. This chiral α-boryl organocopper species then undergoes electrophilic amination with the *O*-benzoylhydroxylamine reagent, generating the corresponding α-amino boronic ester in good yield and excellent enantioselectivity. Extension of this methodology to the aminoboration of alkenyl boronic esters has also been reported.[113] Yun[114] and Hoveyda[115] have recently independently reported a mechanistically related copper-catalyzed enantioselective hydroallylation of alkenyl boronic esters.



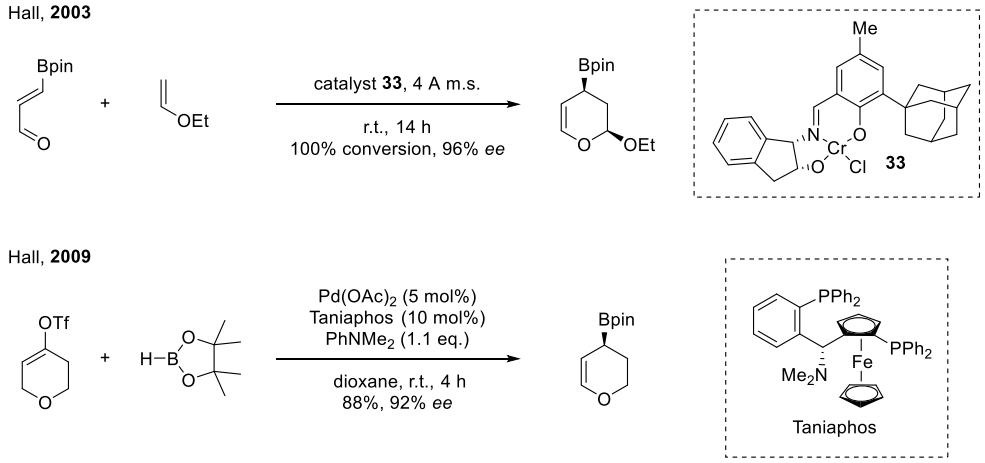
Scheme 31: *Enantioselective copper-catalysed hydrofunctionalization processes.*

Fu and co-workers have recently reported an elegant nickel-catalysed transformation for the asymmetric synthesis of alkyl boronic esters that is also likely to proceed through a chiral α-boron-alkylmetal intermediate.[116] Racemic α-haloalkyl boronic esters undergo coupling with a variety of organozinc reagents by using a nickel–chiral diamine catalyst system to provide alkyl boronic esters in excellent yields and levels of enantiocontrol (Scheme 32). Initial transmetalation with the organozinc reagent generates alkyl-nickel(I) species **31**. Homolytic cleavage of the α-haloalkyl boronic ester C–Cl bond, followed by recombination provides dialkyl-nickel(III) species **32**, which then undergoes reductive elimination generating the chiral alkyl boronic ester and the catalytically active nickel(I) complex.



Scheme 32: *Fu's enantioselective nickel-catalysed synthesis of alkyl boronic esters.*

A completely mechanistically distinct method to access enantioenriched alkyl boronic esters through the transformation of boron-containing prochiral substrates was reported by Hall and co-workers in 2003.[117] Using 3-boryl acrolein as the heterodiene, Hall and co-workers described a highly enantio- and diastereoselective chromium(III)-catalysed inverse-electron-demand hetero[4+2] reaction (Scheme 33). Using chiral tridentate Schiff base chromium complex **33** they could access cyclic allyl boronic esters in excellent levels of enantiocontrol. The nature of this inverse-electron-demand hetero[4+2] reaction limits the allyl boronic ester products formed to those containing an acetal functionality. Keen to develop a method that accesses a broader range of enantioenriched cyclic allyl boronic esters, Hall and co-workers later developed an asymmetric palladium-catalysed tandem isomerisation – Miyaura borylation process (Scheme 33).[118] Stereodetermining hydropalladation followed by β-hydride elimination and stereospecific and regioselective palladium-catalysed borylation of the resulting allylic triflate provides the pyranyl allylic boronic esters in good yield and enantioselectivity.

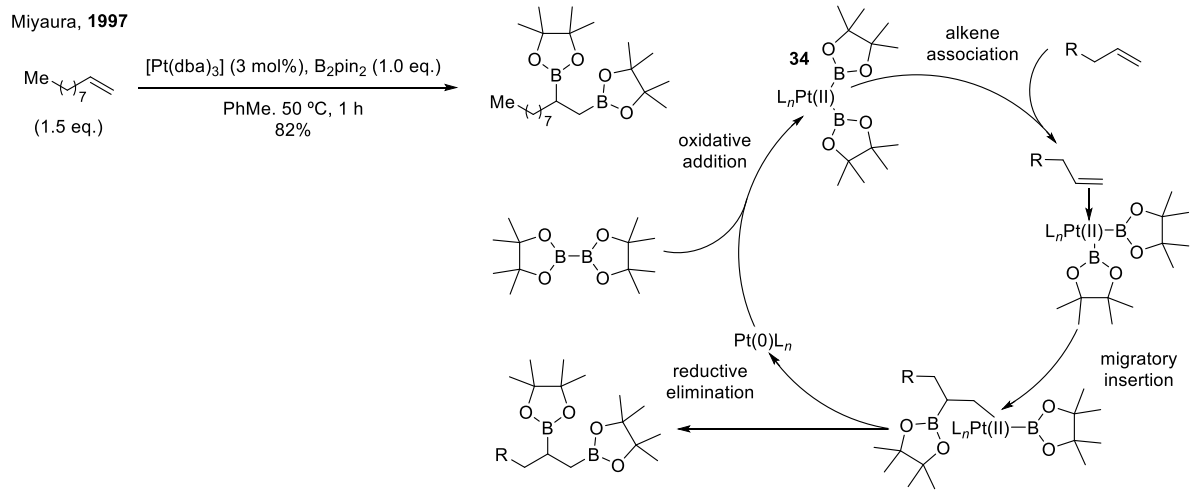


Scheme 33: *Hall's enantioselective chromium-catalysed inverse-electron-demand hetero[2+4] reaction and palladium-catalysed isomerisation–Miyaura borylation of vinyl triflates* .

8. *Transition-Metal-Catalysed Diboration*

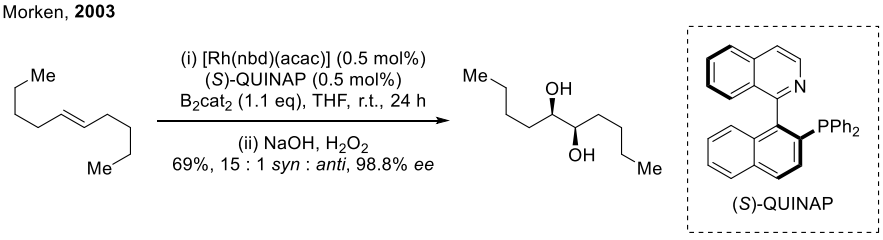
The methods described in the preceding sections have generated a single stereogenic boron-bearing centre. However, methods that introduce two alkyl boryl groups in a single transformation would be of immense value. As will become clear, the two boryl groups often have differing electronic or steric character, allowing for subsequent orthogonal functionalization.

The first efficient platinum-catalysed diborations of alkenes with diboron reagents were reported independently in 1997 by the groups of Miyaura[119] and Smith III.[120] Baker and co-workers had, two years previously, reported a gold-catalysed alkene diboration,[121] but such systems have been shown to be much more reluctant to be rendered asymmetric.[122] The mechanism proposed by Miyaura and co-workers is generally thought to be the mechanism for a wide variety of transition-metal-catalysed diboration processes; oxidative addition of B_2pin_2 to a platinum(0) complex provides platinum(II) complex **34**, which inserts into the alkene, installing the Bpin group and the alkyl–platinum(II)–boron moiety, which then undergoes carbon–boron bond-forming reductive elimination, releasing the diborated product and regenerating the catalytically active platinum(0) species (Scheme 34). Rhodium(I)-catalysed diboration processes have also been described and are thought to proceed by a related oxidative-addition–insertion–reductive elimination catalytic cycle.[123,124]



Scheme 34: *Platinum-catalysed diboration of alkenes with B_2pin_2.*

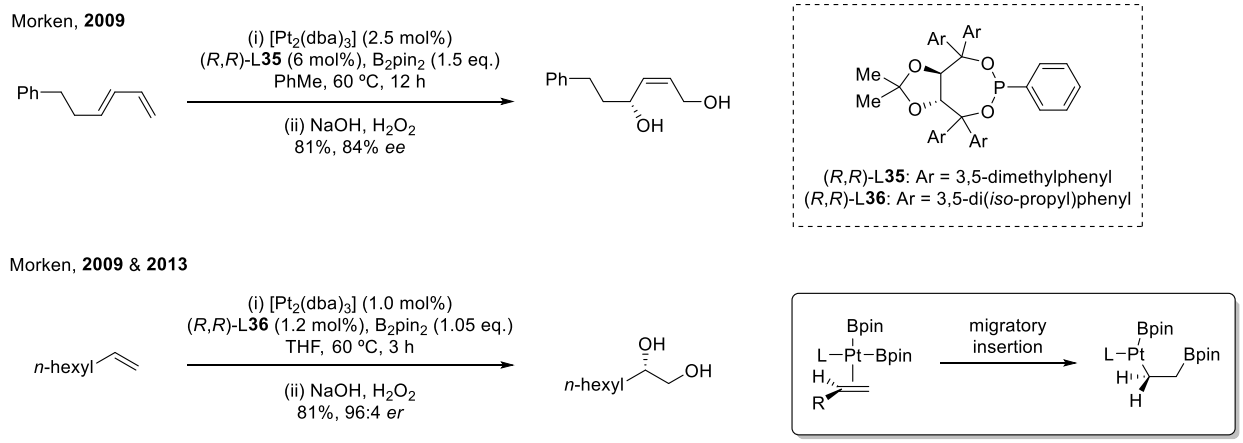
While Norman and Marder reported moderate levels of diastereoselectivity in the platinum(0)-catalysed addition of chiral diboron reagents across alkenes,[125] the major breakthrough in stereoselective diboration reactions came with a report from Morken in 2003 (Scheme 35).[126] Using the chiral N,P ligand, QUINAP, in combination with a cationic rhodium(I) complex, the authors reported excellent levels of asymmetric induction in the diboration of a range of internal *E*-alkenes (diminished stereocontrol, however, was observed for the corresponding *Z*, terminal, and 1,1-disubstituted olefins). A later study by the same group established that increasing the steric bulk adjacent to the terminal alkene (generally to a quaternary centre) allows diboration of these substrates in synthetically useful levels of enantioselectivity, providing molecules that contain both a primary and a secondary alkyl boronic ester possessing different reactivity profiles.[127,128]



Scheme 35: *Morken's enantioselective rhodium-catalysed diboron of 1,2-disubstituted alkenes.*

Morken and co-workers also reported the first ligand-controlled asymmetric platinum(0)-catalysed diboration reactions. Using chiral TADDOL-derived phosphoramidite ligands in combination with

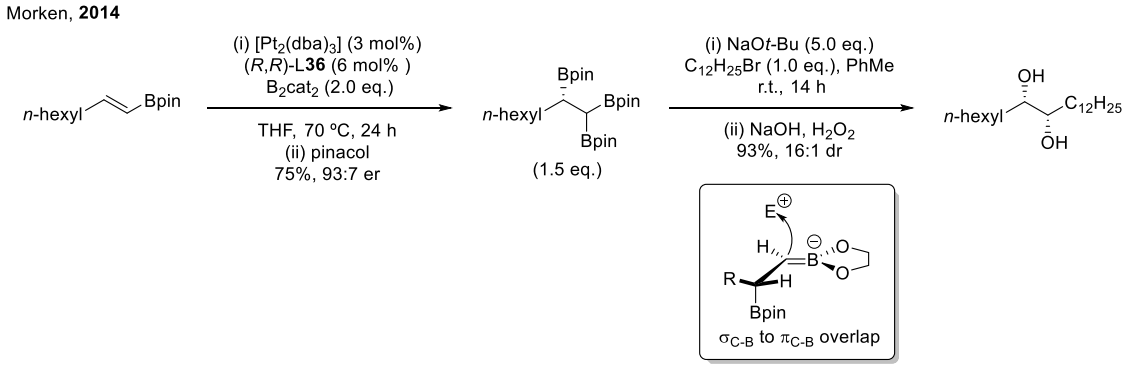
$Pt_2(dba)_3$, the asymmetric diboration of allenes, dienes and terminal alkenes was achieved. In their first publication, they described the 1,4-diboration of 1,3-dienes with excellent levels of stereocontrol (Scheme 36).[129] The authors noted, however, that when one terminus of the diene was disubstituted, 1,2-diboration of the less sterically hindered alkene was observed. This observation was harnessed in a later publication for the enantioselective 1,2-diboration of 1,3-dienes, providing access to the valuable chiral allyl boronic ester motif, which can participate in a subsequent allylation of carbonyl compounds with complete transfer of chirality.[130] Further drawing on this 1,2-diboration observation, Morken later showed that terminal alkenes could undergo highly enantioselective diboration under similar conditions.[131,132]



Scheme 36: *Morken's enantioselective platinum-catalysed diboration of dienes and terminal alkenes.*

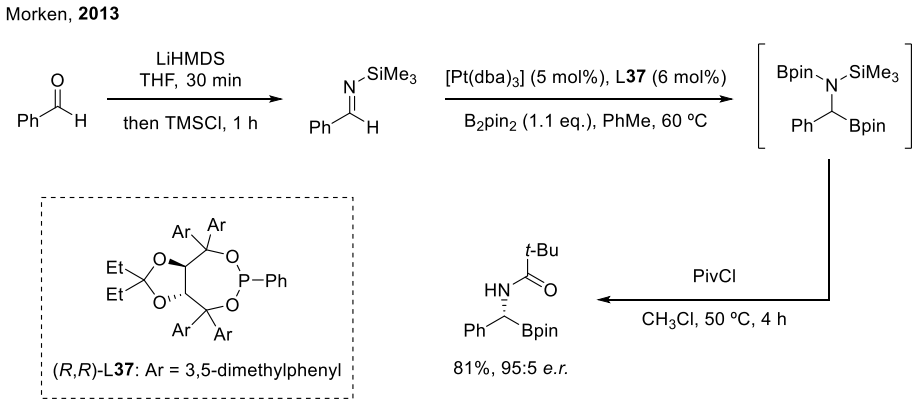
Morken later reported the asymmetric platinum(0)-catalysed diboration of vinyl boronic esters giving access to enantioenriched tris(boronic esters) (Scheme 37).[133] These tris(boronic esters) could then undergo stereoselective deborylative alkylation, thus accessing the *syn* 1,2-diols in excellent diastereomeric ratios. Notably, this two-step process provides products of a formal asymmetric 1,2-diboration of internal alkenes, a transformation not yet achievable directly under platinum catalysis. The authors also note that these tris(boronic esters) undergo deborylative alkylation under milder conditions than those required for the parent geminal bis(boronic esters). They attribute this increased reactivity to interaction of the electron rich C–B σ bond with the C=B π-type bond formed upon

deborylation; this interaction not only increases the nucleophilicity of the π bond, but also leads to approach of the electrophile on the opposite face to the C–B σ bond, leading to the relative configuration observed in both inter- and intramolecular alkylations.



Scheme 37: *Morken's enantioselective platinum-catalysed diboration of alkenyl boronic esters.*

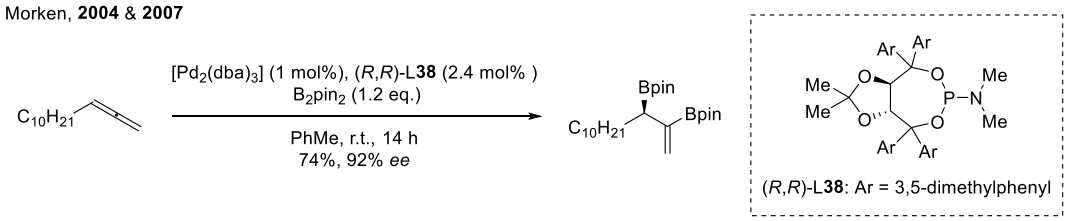
Following the report of an earlier non-stereoselective transformation by Baker and co-workers,[134] Morken reported the enantioselective one-pot aminoboration of aldehydes by using a platinum/phosphonite catalysis system, providing access to valuable α-amino boronic esters (Scheme 38).[135] The reaction involves the in-situ formation of *N*-silyl imines from the reaction of an aldehyde and LiHMDS, followed by platinum-catalysed asymmetric diboration. The α-amino boronic esters were then isolated as the *N*-acyl derivative through reaction with pivaloyl chloride.



Scheme 38: *Morken's enantioselective platinum-catalysed aminoboration of aldehydes.*

One further metal has been used for efficient diboration reactions through a redox-based catalytic cycle. Morken and co-workers published extensive studies into the palladium-catalysed diboration of allenes.

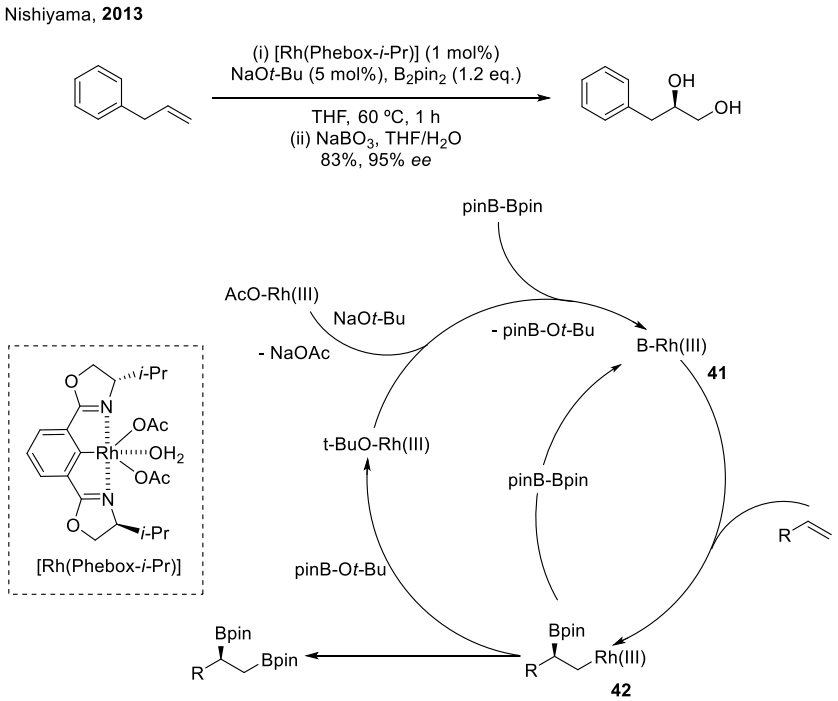
As for the platinum-based systems, they used phosphoramidite-based ligands in combination with palladium(0) salts to achieve excellent levels of enantioselectivity for the diboration of the internal π system of a range of allenes (Scheme 39).[136,137] This transformation provides access to valuable products containing both a vinylic and an allylic boronic ester.



Scheme 39: *Morken's palladium-catalysed diboration of allenes.*

The transformations described above all make use of a transition-metal redox cycle comprising oxidative addition–insertion–reductive elimination. Redox neutral pathways, however, have also been invoked for transition-metal-catalysed diboration processes. In 2007, Fernandez and co-workers reported a copper(I)/NHC-catalysed process for the diboration of styrene.[138] Although not stereoselective and limited in scope, the reaction represents an important alternative mechanistic pathway towards diboration. DFT calculations disfavour an oxidative-addition pathway and support a transmetalation-type event generating a neutral copper(I)–boryl species. Insertion of the alkene installs the first boryl group and generates an alkyl–copper(I) species, which then undergoes further transmetalation with the diboron reagent providing the diboration product and the catalytically active copper(I)–boryl species. A further report by Fernandez on a diboration reaction using palladium(II) salts in combination with NHCs is also thought to follow a redox-neutral pathway involving transmetalation of the palladium(II) centre with the diboron reagent.[139] A related mechanism was reported by Nishiyama and co-workers in their rhodium(III)-catalysed asymmetric diboration of terminal alkenes (although they do not rule out the possibility of a rhodium(I)–rhodium(III) mechanism).[140] Using chiral rhodium[bis(oxazolinyl)phenyl] ligands, excellent reactivity and enantioselectivity could be achieved for a range of terminal alkenes, including alkenes without an adjacent activating arene group (Scheme 40). Catalytic sodium *tert*-butoxide was found to be essential

for reactivity and is proposed to facilitate the generation of a boryl–rhodium(III) species **41** and a pinB–O*t*-Bu adduct by a σ-bond metathesis or transmetalation event. Insertion of the alkene then installs the boron moiety and generates a rhodium(III)–alkyl species **42**, which undergoes σ-bond metathesis or transmetalation with the previously formed pinB–O*t*-Bu adduct providing the diboration product and regenerating the active *t*-BuO–rhodium(III) species (alternatively, the rhodium(III)–alkyl species **42** may undergo direct transmetalation with the diboron reagent, generating the boryl–rhodium(III) species **41** directly).

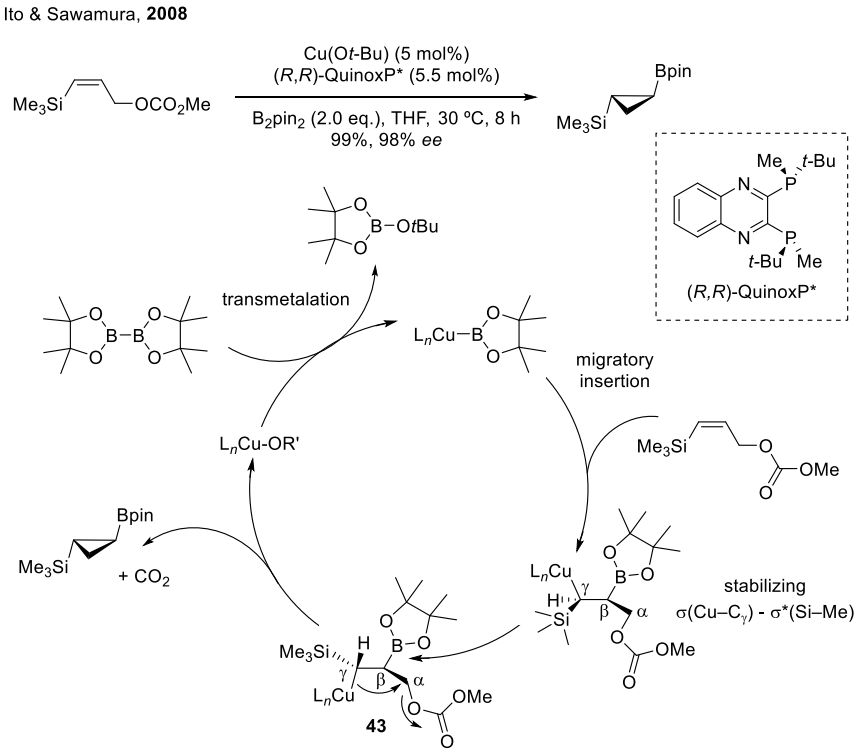


Scheme 40: *Nishiyama's enantioselective rhodium-catalysed diboration of terminal alkenes.*

9. *Transition-Metal-Catalysed Borylative Difunctionalization Reactions of Alkenes*

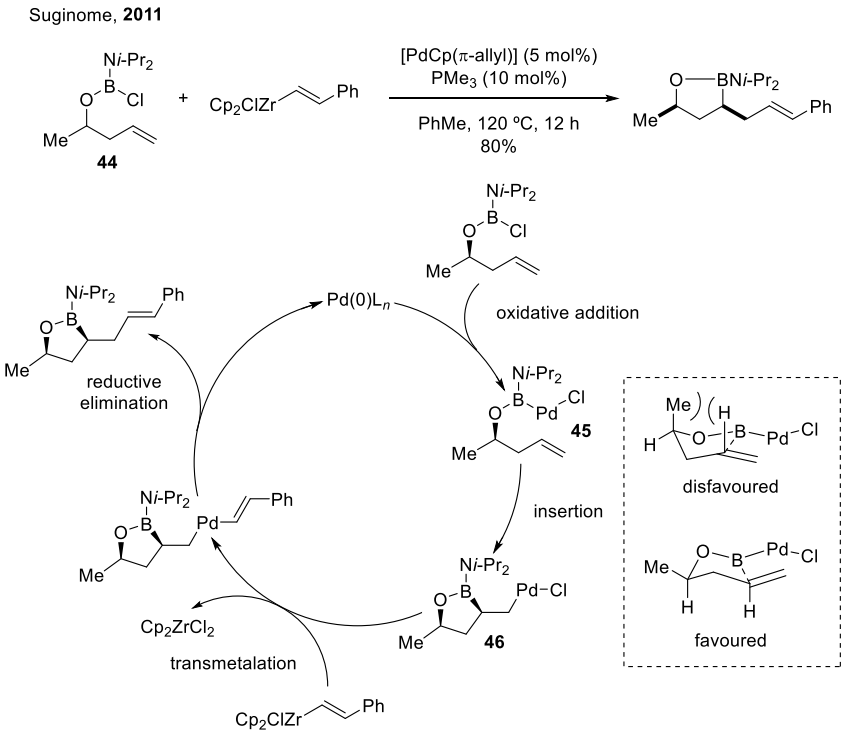
All of the above diboration reactions start with the insertion of an alkene into a metal–boryl bond. The resultant β-boryl alkyl metal species then undergoes either a further transmetalation or a reductive elimination step to generate the desired diboration products. A number of groups have recognised the potential of intercepting this β-boryl alkyl metal species to access alternative difunctionalization products. Some of the following methods are yet to be rendered asymmetric, but warrant discussion in terms of mechanism and their potential to be developed into efficient asymmetric methods for the synthesis of highly functionalized chiral alkyl boronic esters.

In 2008, Ito and Sawamura reported the highly diastereo- and enantioselective copper-catalysed transformation of γ-silylated allylic carbonates into cyclopropyl boronic esters in the presence of B_2pin_2 (Scheme 41).[141] The reaction is proposed to start with the insertion of a copper–boryl species into the double bond such that the boryl group is positioned β to the carbonate and the copper–alkyl bond is in the γ position, stabilised by the adjacent σ*(C–Si). Intermediate **43** is now set up for intramolecular displacement of the carbonate and the generation of the desired boryl-substituted cyclopropane. For the *Z*-allylic carbonates, excellent levels of *trans*-diastereoselectivity and enantioselectivity were observed by using chiral diphosphine ligand QuinoxP* or Segphos (*E*-allylic carbonates were obtained with slightly lower levels of *trans*/*cis* selectivity). The authors later established that γ-substitution of allylic electrophiles with an aryl group in place of the silyl group also directed the regioselectivity of the Cu–B insertion such that aryl-substituted cyclopropyl boronic esters could be accessed in high levels of enantioinduction.[142] The use of silyl- and aryl-substituted homoallylic electrophiles also allowed access to the corresponding cyclobutyl boronic esters through an analogous mechanism, although the asymmetric variant was not reported.[143] A copper-catalysed borylative exo-cyclisation was also reported for homoallylic bromides.[144]



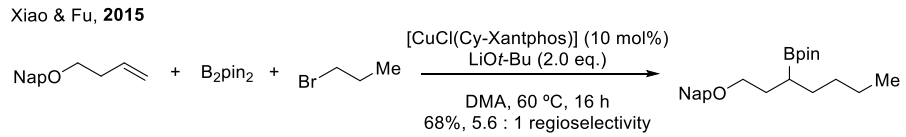
Scheme 41: *Ito and Sawamura's copper-catalysed borylative cyclisation.*

Suginome and co-workers have reported a palladium-catalysed borylative cyclisation.[145] Chloroboryl ethers such as **44** were subjected to reaction with alkenylzirconium reagents under palladium/phosphine catalysis to provide the alkenylboration products in moderate to good yields (Scheme 42). Initial oxidative addition of the boron–chlorine bond to the palladium(0) catalyst generates a palladium(II)–boryl species **45**, which undergoes insertion into the proximal alkene, introducing the boryl moiety and a palladium(II)–alkyl species. This palladium(II)–alkyl species **46** then undergoes transmetalation with the alkenylzinc reagent, followed by reductive elimination to provide the difunctionalization product and the catalytically active palladium(0) complex. Although asymmetric variants were not investigated, the reaction exhibits excellent levels of diastereoselectivity, the sense of which are attributed to a chair-like transition state in the insertion step.



Scheme 42: *Suginome's palladium-catalysed alkenylboration.*

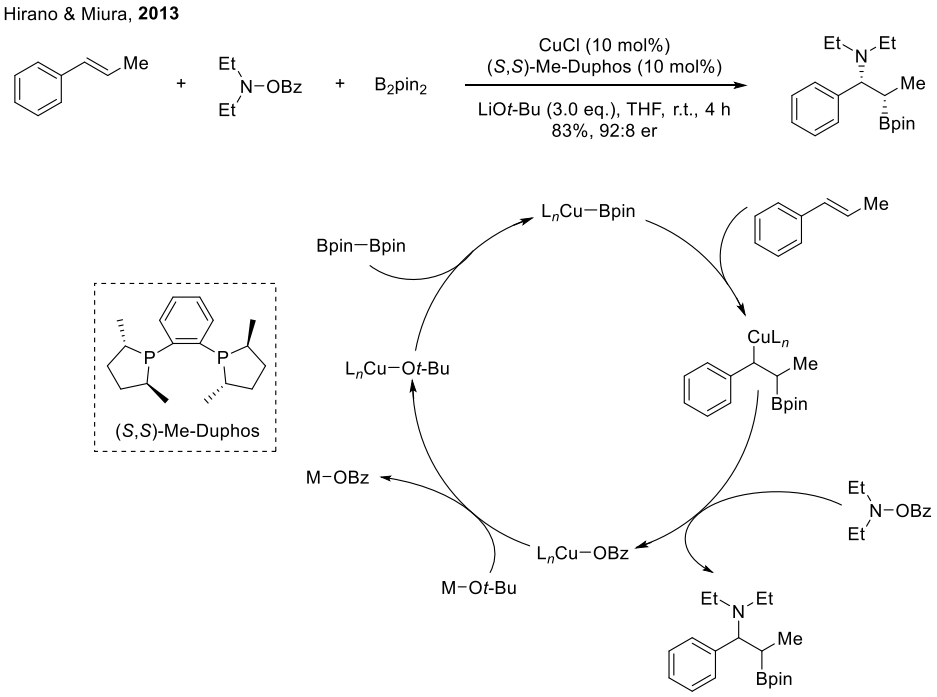
β-Boryl alkyl copper species derived from insertion of a copper–boryl species into a double bond have also been functionalized through intermolecular processes. In 2014, Yoshida reported a copper-catalysed three-component carboboration of terminal alkenes.[146] Using benzyl chlorides as activated electrophiles in combination with B_2pin_2, the alkylboration products could be obtained in moderate yields. The regioselectivity of the initial insertion, however, leads to a primary alkyl boronic ester. In an interesting development, Xiao and Fu later reported a related copper-catalysed alkylboration of terminal alkenes by using simple, unactivated, alkyl halides.[147] Importantly, they could invert the regioselectivity of the insertion through a change in ligand, allowing access to the secondary alkyl boronic esters (Scheme 43). These reactions are currently limited to alkenes possessing a coordinating heteroatom; the authors postulate that this group accelerates the insertion of CuBpin across the alkene, competing with deleterious side reactions such as the direct borylation of the alkyl electrophile.



Scheme 43: *Copper-catalysed alkylboration of terminal alkenes.*

Using cooperative palladium/copper catalysis, the group of Semba and Nakao,[148] Brown,[149,150] and Liao[151] have also independently reported the carboboration of a variety of alkenes. The intersection of the two transition metal cycles occurs through a key transmetalation of the β-boryl alkyl copper species with an organopalladium species followed by reductive elimination. In the majority of examples, however, a terminal alkene is used and insertion occurs to position the boryl moiety at the terminal position, thus precluding the generation of chiral alkyl boronic esters. Brown has, however, reported the copper/palladium-catalysed arylboration of internal alkenes, generating secondary alkyl boronic esters.[149,150] This process has recently been rendered asymmetric through the use of a chiral NHC–copper complex.[152]

Another area of intense research interest in recent years has been the copper-catalysed aminoboration of alkenes. In 2013, Miura and Hirano reported the copper-catalysed aminoboration of styrene derivatives with B_2pin_2 and *O*-benzoyl-*N*,*N*-dialkylhydroxylamines, where the transient borylated alkyl–copper species is proposed to undergo electrophilic amination with the *O*-benzoylhydroxylamine (Scheme 44).[153] Preliminary studies indicate that good levels of enantioenrichment of the 1,2-aminoborated products can be achieved through the use of chiral diphosphine Duphos-type ligands. The methodology was later extended to facilitate the aminoboration of bicyclic alkenes,[154] methylenecyclopropanes,[155] vinylsilanes,[156] and unactivated terminal alkenes.[157] Tortosa has also used this reactivity platform for the aminoboration of cyclopropenes.[58]



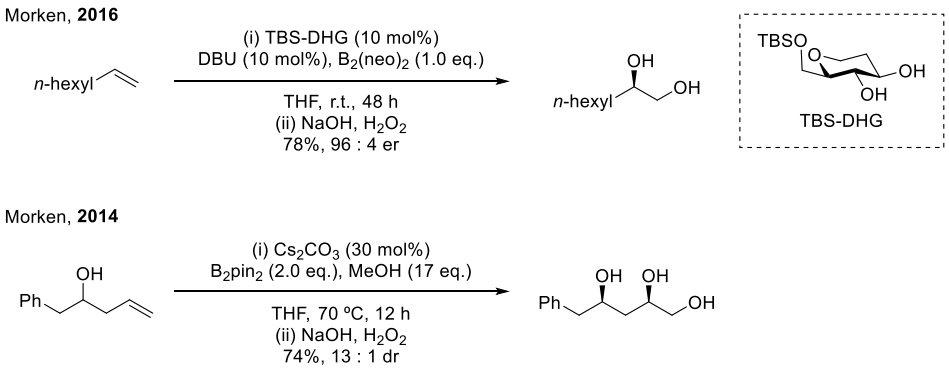
Scheme 44: *Copper-catalysed enantioselective aminoboration of styrene derivatives*.

Borylated alkyl–copper species have also been trapped with aldehydes and ketones,[158] imines,[159,160,161] Michael acceptors,[162] and allylic electrophiles,[163] although both the nature of the substrate π-system (allenes and terminal dienes as opposed to internal or activated alkenes) and the regioselectivity of the initial insertion means that secondary alkyl boronic esters are not accessed.

10. *Transition Metal-Free Diboration*

In Section 5 (*Transition-Metal-Free Boration of Electron-Deficient Alkenes*) we described the developments in the protoboration of electron-deficient alkenes under metal-free conditions. In these studies, catalytic quantities of Lewis basic small molecules (NHCs, phosphines) were used to activate the diboron reagent, whereby association with one of the boron atoms renders the other sp^2 boron atom nucleophilic and capable of attacking the electron-deficient π system. Although in such systems the resultant anionic intermediate is quenched by a proton source, following a report by Fernandez and co-workers in 2011, it has been recognised that the second boryl moiety of the diboron reagent can act as

the electrophilic quenching reagent, leading to a diboration process.[164] In the system reported by Fernandez, methoxide anion (generated from the crucial base and methanol additives) is proposed to activate the diboron reagent, generating an sp^2–sp^3 diboron species. In a later publication, Fernandez was able to achieve moderate levels of enantioselectivity (up to 42% *ee*) for the diboration of unactivated terminal olefins, through the use of chiral alcohol additives.[165] The chiral alkoxides presumably interact with the diboron reagent, allowing for moderate level of asymmetric induction. Morken and co-workers later considerably improved the asymmetric metal-free diboration of alkenes through the use of chiral diols.[166] Using catalytic quantities of a chiral diol (carbohydrate derivatives were found to induce the highest levels of enantioselection) and base with the neopentylglycolate diboron reagent, $B_2(neo)_2$, the asymmetric diboration of a variety of alkenes in excellent levels of enantioselectivity was achieved (generally above 96:4 er) (Scheme 45). Interestingly, styryl derivatives gave lower enantioselection, as did 1,2-disubstituted alkenes. A stereoselective diboration was also reported by Morken and co-workers, in which homoallylic alcohols could undergo diboration with high levels of diastereoselectivity, providing the 1,2-*syn* diols in good yield following oxidative work-up.[167] In this process the homoallylic alkoxide is thought to interact with the diboron reagent, activating it towards transfer of the two boryl groups to the alkene and directing it towards one face of the olefin π system.

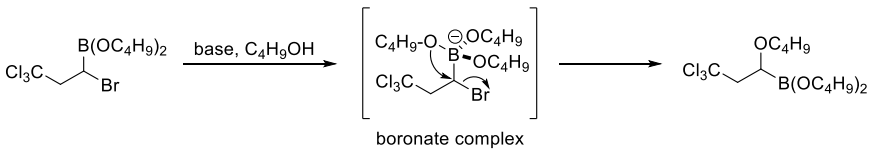


Scheme 45: *Morken's transition metal free alkene diboration.*

11. *1,2-Metallate Rearrangements of Boronate Complexes*

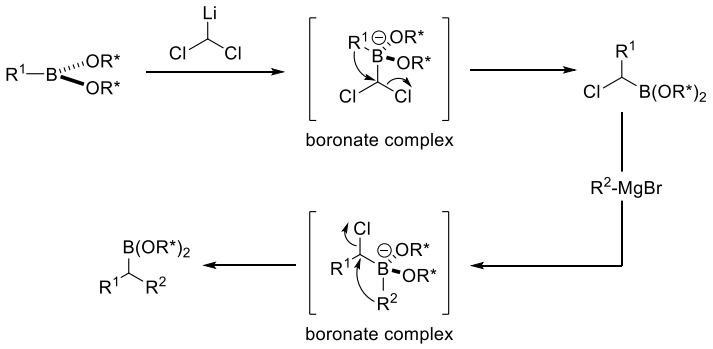
Reflecting the immense variety of reactivity exhibited by boron, another method draws initially on the electrophilic nature of the boron centre, derived from its empty p orbital, followed by the propensity of the boronate complex, which results from attack of a nucleophile, to undergo stereospecific 1,2-metallate rearrangement with expulsion of a leaving group α to the boron atom.

In the early 1960s, Matteson and Mah reported a study into *Neighbouring Boron in Nucleophilic Displacement*.[168] In this report, they described the displacement of the halide ion from α-haloalkyl boronic esters by a variety of nucleophiles. A considerable rate acceleration was observed for the displacements with α-haloalkyl boronic esters when compared to the S_N2 displacement reactions of traditionally activated electrophiles such as allyl bromides. This observation led to the proposal of an alternative mechanism for the displacement, involving the initial attack at the electrophilic boron atom by the nucleophile forming a 4-coordinate boron anion (a boronate complex), followed by 1,2-migration of one of the ligands on boron to the electrophilic α carbon atom with expulsion of the bromide ion (Scheme 46).



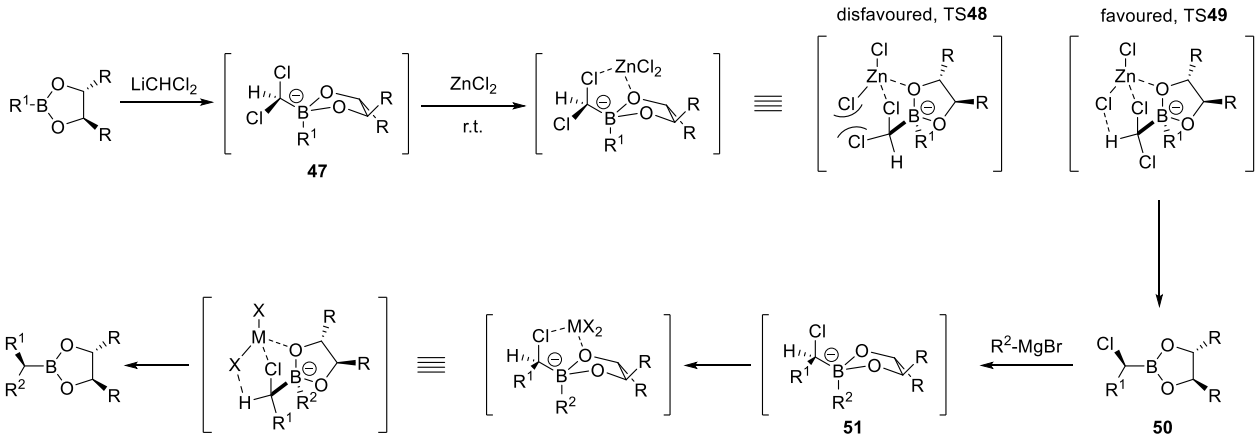
Scheme 46: *Nucleophilic displacement of halide from α-haloalkyl boronic esters.*

Almost twenty years later Matteson and co-workers harnessed this reactivity platform in developing a highly effective asymmetric method for the synthesis of chiral boronic esters.[169,170] Key to the strategy was the use of a chiral auxiliary within the diol moiety of the boronic ester. A two-step strategy was developed comprising (i) addition of dichloromethyllithium ($LiCHCl_2$) to the chiral boronic ester providing an α-haloalkyl boronic ester with high levels of diastereocontrol, and (ii) addition of a second organometallic reagent (generally a Grignard) to provide the desired alkyl boronic ester (Scheme 47).



Scheme 47: *Matteson's synthesis of chiral boronic esters using a chiral diol auxiliary.*

Studies from Matteson's group over the following years established that the introduction of sub-stoichiometric quantities of zinc chloride accelerated the reaction and considerably improved the observed levels of diastereoselectivity.[171] The groups of Corey[172] and Midland,[173] proposed a model that accounts for the observed stereocontrol and the promoting effects of zinc chloride (Scheme 48).



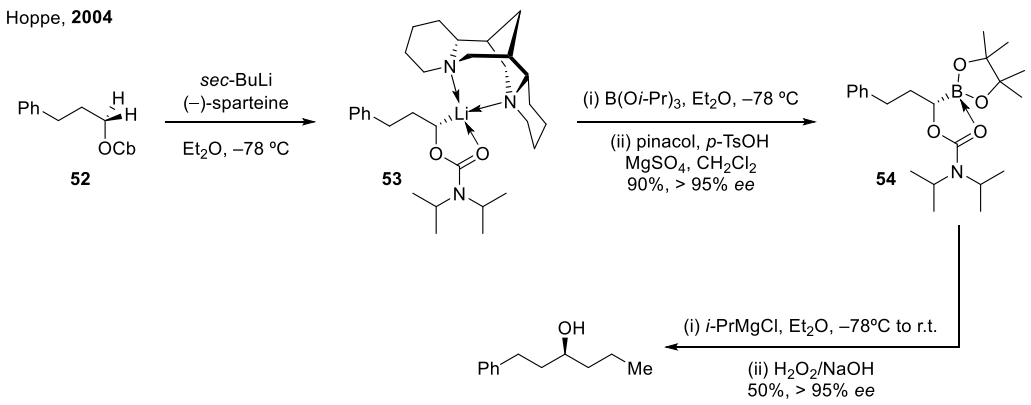
Scheme 48: *Rational for observed diastereoselectivities.*

Following formation of boronate complex **47**, zinc chloride is proposed to coordinate to the more accessible of the diol ligand oxygen atoms and one of the two diastereotopic chlorine atoms, generating one of two transition state structures TS**48** or TS**49**. Structure TS**49** is stabilised by an additional interaction between the chloride of zinc chloride and the C–H bond (Scheme 48). In structure TS**48** no such interaction is possible and this pathway is disfavoured. Proceeding via structure TS**49**, migration of R^1, which is attached to the boron atom, displaces the antiperiplanar chlorine atom as chloride, thus

generating α-chloroalkyl boronic ester **50** with high levels of stereocontrol. Treatment of this species with a Grignard or alkyl lithium generates a second boronate complex **51**. The subsequent migration of R^2 is now stereospecific, as there is only one chlorine atom remaining and migration must again proceed through antiperiplanar alignment of the migrating and leaving groups.

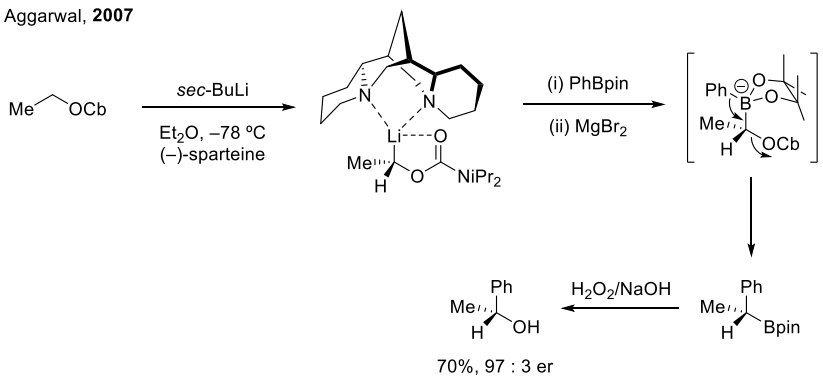
Although Matteson, and others, established the synthetic utility of this process in a number of elegant natural product and pharmaceutical syntheses,[174,175,176] its potential as a strategy for iterative homologation and the introduction of multiple stereocentres is limited by one key aspect: the reaction proceeds under *substrate control*. The stereochemical course of the homologation is controlled by the chirality of the diol. Access to the opposite stereoisomer requires exchange of the diol for its enantiomer, a process that involves additional steps.

In 2004 Hoppe and co-workers developed a related strategy for the asymmetric synthesis of chiral boronic esters, but this process proceeded under reagent control.[177] Hoppe showed that alkyl carbamates, such a **52**, could be deprotonated enantioselectively with the chiral base *sec*-butyllithium/(−)-sparteine and that the resultant lithium carbenoids **53** were stable at −78 °C. Direct treatment at this temperature with triisopropyl borate, led to the formation of chiral α-carbamoyloxy-alkyl boronic ester **54**, analogous to Matteson's α-haloalkyl boronic esters (Scheme 49). As before, further treatment with Grignard or organolithium reagents provided the expected boronate complexes, followed by stereospecific 1,2-migration, expulsion of the carbamoyloxy moiety and the generation of a new secondary chiral alkyl boronic ester. This method was quickly adopted by Kocienski and co-workers for the introduction of a chiral secondary amine in their total synthesis of (−)-*N*-acetylcolchinol.[178] Although Hoppe's method does proceed under reagent control, it still requires two steps to accomplish the homologation.



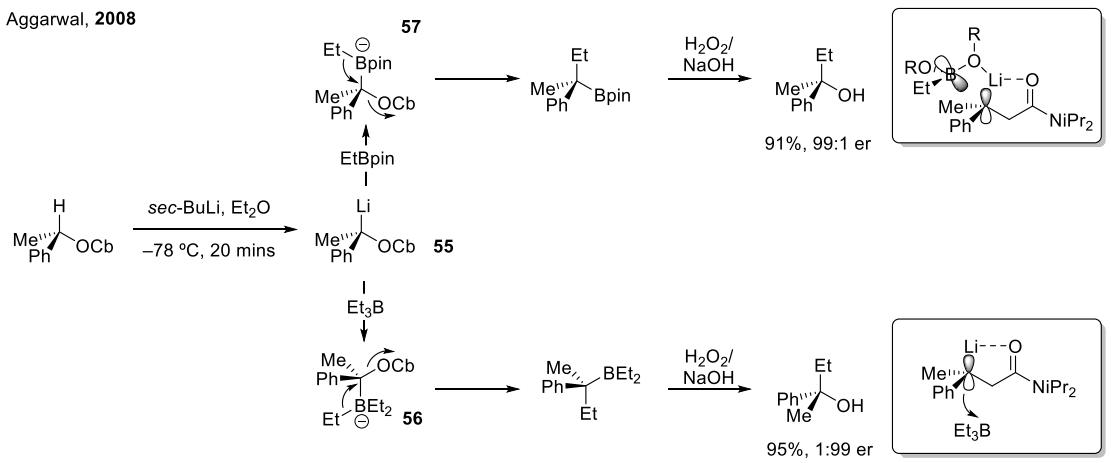
Scheme 49: *Hoppe's asymmetric deprotonation and trapping with triisopropyl borate.*

In 2007, Aggarwal and co-workers developed a related strategy, in which they exploited the direct reaction of Hoppe-type chiral lithiated carbamates with boranes and boronic esters as a route to enantioenriched alkyl boronic esters (Scheme 50).[179] Not relying on the stepwise approach of Hoppe, this methodology represents a direct method for iterative synthesis. Extensive studies over the last decade have extended its scope and deeper mechanistic understanding has enabled the homologation of previously difficult substrates. Specifically, some boronate complexes were found to be slow to undergo 1,2-metallate rearrangement, resulting in diminished yields. Although Lewis acids, such as magnesium bromide, were found to promote the 1,2-metallate rearrangement, Aggarwal later reported that the use of α-lithiated alkyl 2,4,6-triisopropylbenzoates (TIB esters) greatly accelerated the rate of the 1,2-metallate rearrangement and significantly increased the scope of the homologation methodology.[180]



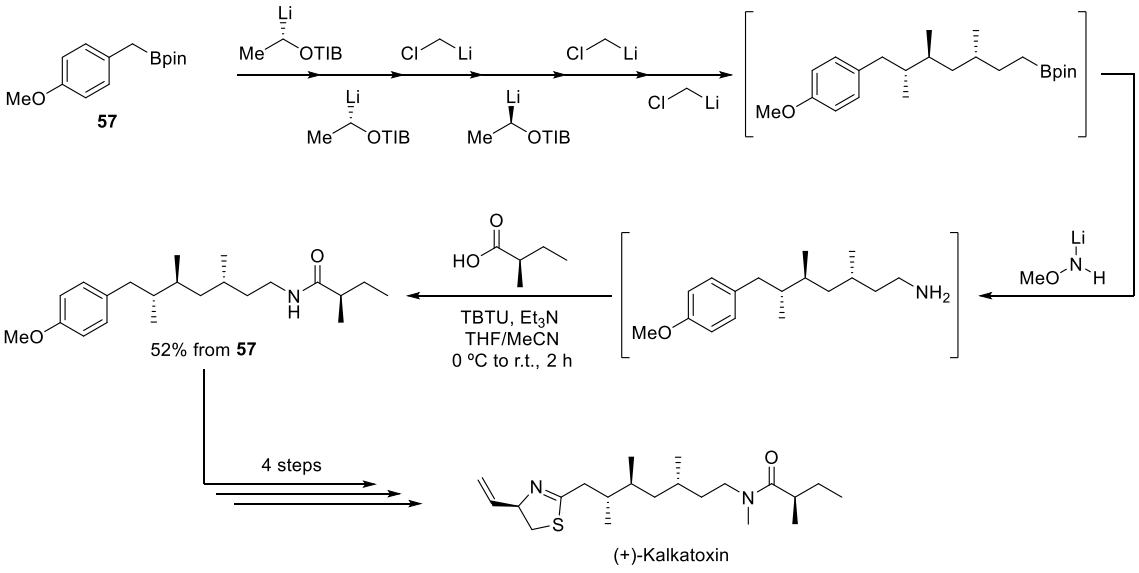
Scheme 50: *Aggarwal's iterative lithiation–boryaltion strategy.*

A major limitation of the Matteson homologation is that it fails to provide access to tertiary boronic esters. In an important breakthrough in 1,2-metallate-based transformations, Aggarwal and co-workers extended their methodology to incorporate secondary chiral lithiated carbamates, which, when reacted with a borane or boronic ester, provided the corresponding tertiary alkyl boronic esters in excellent levels of enantiocontrol (Scheme 51).[181] Oxidation then furnished the highly enantioenriched tertiary alcohols, which are valuable motifs in a variety of biologically active molecules and difficult to access by other methods. Interestingly, use of boranes in place of boronic esters led to a different stereochemical outcome; reaction of the secondary chiral lithiated carbamate **55** with a range of boranes to form the boronate intermediate **56** proceeded with inversion of configuration, while the corresponding reactions with boronic esters led to boronate intermediate **57** with retention of configuration. When boronic esters are used, complexation of the lithium of the metallated carbamate with the boronic ester oxygen atom delivers the lithium carbenoid to the same face (Scheme 51). In the absence of this interaction, as in the case of boranes, reaction occurs on the opposite face to the metal, a face that has a relatively high level of electron density owing to the somewhat flattened structure of the tertiary benzylic anion (lacking this benzylic stabilisation, lithium carbenoids derived from non-benzylic primary alcohols retain an essentially sp^3-hybridized structure and reaction with both boronic esters and boranes leads to retention of configuration). Further studies established protocols to obtain tertiary boronic esters across a range of substrates in excellent levels of stereocontrol.[182,183,184,185,186]



Scheme 51: *Aggarwal's synthesis of enantioenriched tertiary boronic esters.*

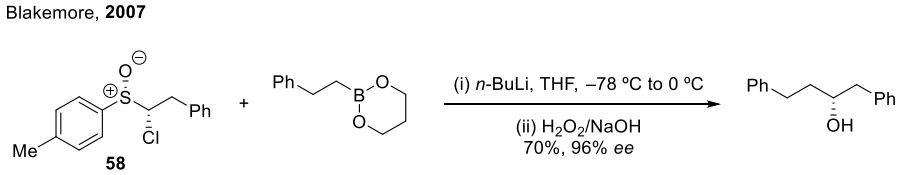
This methodology has also found significant success in the synthesis of natural products and its amenability to iteration has allowed for the development of strategies that allow for the installation of up to ten contiguous stereocentres with essentially complete diastereo- and enantio-control.[187,188]



Scheme 52: *Lithiation–borylation methodology used in the synthesis of (+)-Kalkatoxin.*

Concurrent to the Aggarwal lithiation–borylation methodology, Blakemore and co-workers were also developing an iterative homologation strategy under reagent control (Scheme 53).[189,190] Blakemore and

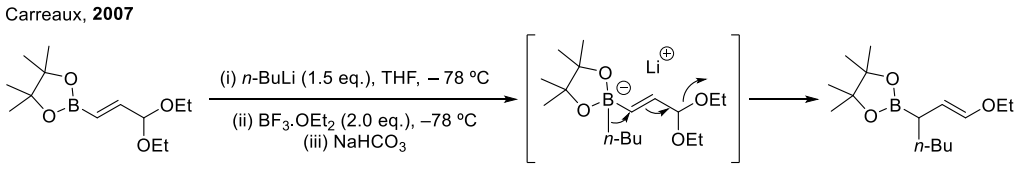
co-workers drew on previous studies by Hoffmann for the generation of highly enantioenriched α-haloalkyl Grignard reagents derived from a magnesium/sulfoxide exchange reaction; key to these early discoveries was the stereospecific nature of the exchange and the stability of the chiral carbenoids at low temperature.[191] Blakemore and co-workers thus postulated that the addition of a configurationally stable Hoffmann carbenoid **58** to a boronic ester would generate the key chiral α-haloalkyl boronate complex. Stereospecific migration of the carbon ligand on boron and expulsion of chloride would then provide the desired chiral alkyl boronic ester. Blakemore and co-workers were able to elegantly realize this strategy by using both magnesium- and lithium-based chiral carbenoids, generated from the corresponding chiral α-chloroalkyl sulfoxides.



Scheme 53: *Blakemore's iterative homologation strategy.*

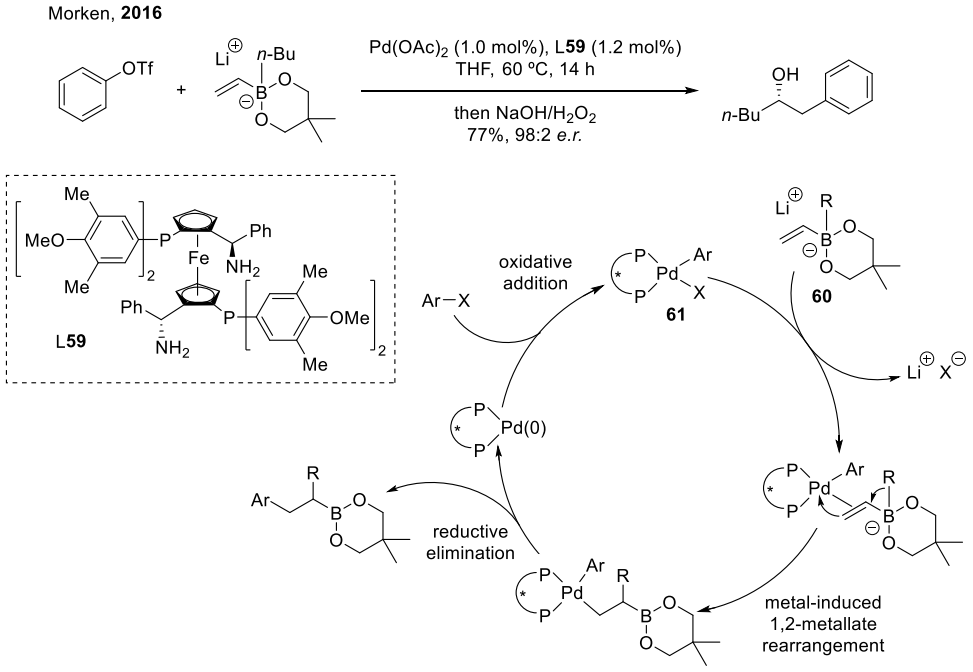
Although the Matteson and Blakemore methods rely on a halide leaving group and Hoppe and Aggarwal make use of a carbamate or benzoate group, earlier work by Aggarwal and co-workers had explored a reagent-controlled asymmetric homologation of boranes by using chiral sulfur ylides. Despite allowing access to secondary boranes in excellent levels of enantioselectivity, the carbenoid-like sulfur ylides were of insufficient reactivity to allow homogation of synthetically useful boronic esters and have thus been somewhat superseded by the lithium carbenoids reagents.[192,193,194]

The 1,2-metallate rearrangements described above are predicated on the presence of a leaving group α to the boron atom. Alternative methods for facilitating such rearrangements can, however, be envisioned. Lombardo[195] and Carreaux[196] have independently described "vinylogous Matteson homologations", where the rearrangement occurs with expulsion of a vinylogous leaving group (Scheme 54). Such processes provide direct access to secondary allyl boronic esters, but stereoselective variants have yet to be described.



Scheme 54: *Vinylogous Matteson homologations.*

In a highly elegant development, Morken and co-workers have described a process in which the 1,2-boronate rearrangement is triggered by activation of a vinyl ligand on boron with an electrophilic species.[197] Morken makes use of an electrophilic aryl–palladium(II) species to trigger the 1,2-metallate shift, where non-racemic chiral ligands on palladium render the overall transformation enantioselective (Scheme 55). Vinyl boronate complex **60**, which can be accessed either by addition of an alkyllithium species to a vinyl boronic ester or the addition of a vinyllithium species to an alkyl boronic ester, undergoes alkene activation by association of an aryl–palladium(II) species **61**, triggering a 1,2-metallate shift and concurrent nucleophilic attack at the palladium(II) centre. Reductive elimination then generates the coupled alkyl boronic ester product and releases the palladium(0) catalyst, ready for subsequent oxidative addition into the aryl triflate bond and closing of the catalytic cycle.

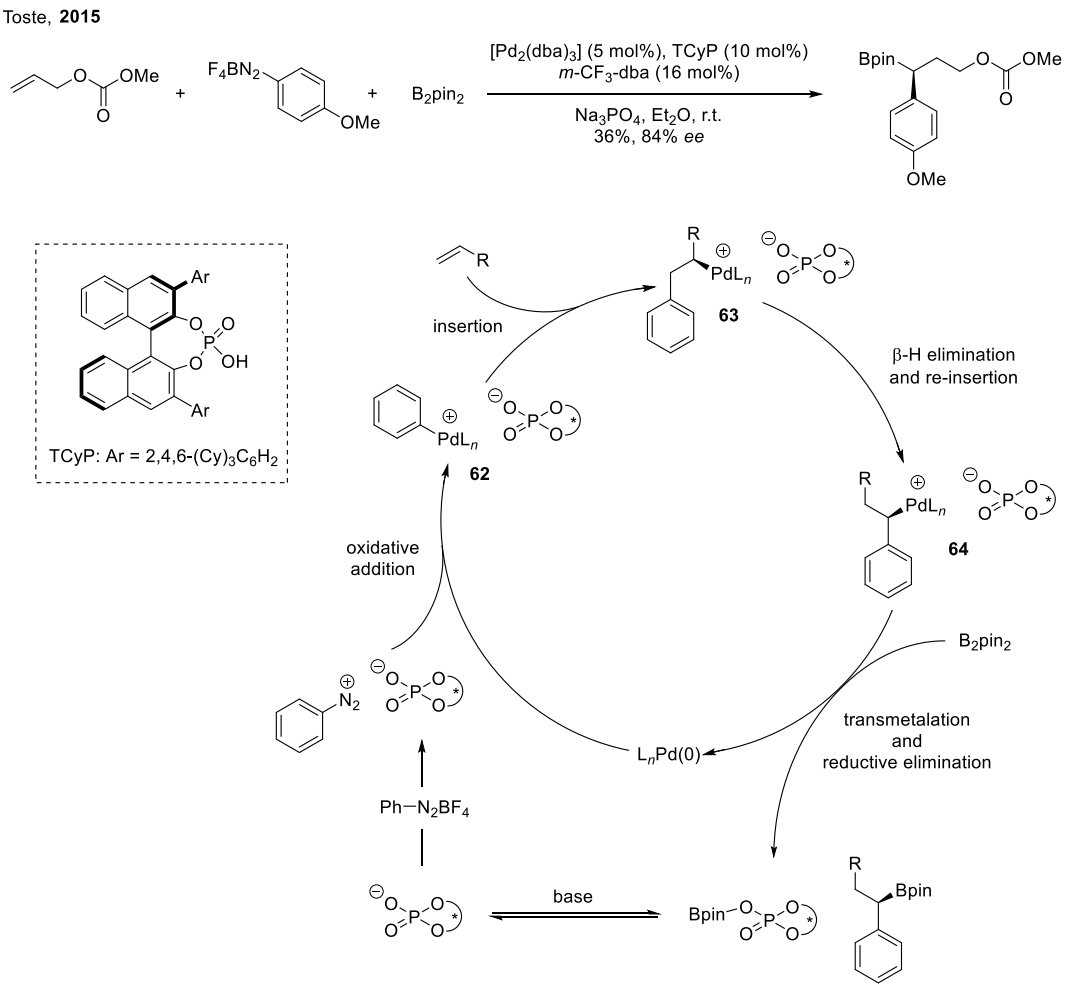


Scheme 55: *Morken's enantioselective palladium-catalysed conjugative cross-coupling.*

12. *Miscellaneous Methods for the Synthesis of Enantioenriched Alkyl Boronic Esters*

Some more recent methods do not fit neatly into the categories established above and yet provide important methods for the synthesis of enantioenriched alkyl boronic esters.

In 2015 Toste and co-workers reported the enantioselective 1,1-arylboration of unactivated alkenes using B_2pin_2 and aryldiazonium salts through the merging of palladium and chiral anion phase-transfer catalysis.[198] Moderate yields and good to excellent levels of enantioenrichment could be obtained for the synthesis of a range of chiral benzylic boronic esters. The authors developed a cascade reaction featuring sequential Heck–Matsuda arylation, re-insertion and Miyaura borylation (Scheme 56). Oxidative addition of the palladium(0) complex into the chiral diazonium salt (rendered soluble by ion pairing with the chiral phosphoric acid) generates palladium(II) species **62**. Insertion of this chiral aryl–palladium(II) species into the terminal olefin provides carbopalladation product **63**. β-Hydride elimination followed by re-insertion provides the benzylpalladium species **64**. Transmetalation with B_2pin_2 followed by reductive elimination then closes the catalytic cycle and provides the enantioenriched benzylic boronic ester.



Scheme 56: *Toste's enantioselective palladium-catalysed 1,1-arylboryation of unactivated alkenes.*

Since Hartwig's seminal publications in 1997[199] and 2000[200] on the direct borylation of unactivated sp^3 C–H bonds by using transition-metal complexes, many types of transition-metal-catalysed C–H borylation methodology have been developed by using iridium, rhodium and ruthenium.[201] Importantly, many of these methods allow the borylation of secondary sp^3 C–H bonds, accessing chiral alkyl boronic esters. More recently, the ligand-directed palladium-catalysed borylation of sp^3 C–H bonds has been reported.[202,203] The direct borylation of sp^3 C–H bonds provides an efficient and highly attractive method for the synthesis of chiral alkyl boronic esters. No methods, however, have yet been shown to be amenable to asymmetric induction. This area of research – the direct asymmetric transition metal-catalysed borylation of sp^3 C–H bonds – will undoubtedly attract intense interest in the coming years.

12. *Conclusions and Outlook*

Although a number of conceptually different methods for accessing non-racemic chiral boronic esters have been presented above, metal-catalysed enantioselective hydroboration of alkenes remains the most attractive entry into this class of molecules owing to the easy access to alkenyl starting materials and the atom-economic nature of the transformation. Therefore, developments in this area will likely have the most impact. As outlined above, efficient and general methods for the enantioselective hydroboration of styrenes (terminal or internal), symmetrical internal alkenes, and α,β-unsaturated carbonyl compounds are available. However, the substrate scope for the hydroboration of non-styrenyl 1,1-disubstituted, trisubstituted, and unsymmetrical 1,2-disubstituted internal alkenes remains narrow and somewhat ill-defined. The high levels of regio- and enantioselectivity observed in the hydroboration of subsets of these types of alkenes, selectivity that has its origins in the presence of directing groups and subtle inductive electronic effects, bodes well for the onward chartering of this challenging area of chemical space. Such a community endeavour should eventually lead to a predictive model that will allow the enantio- and regioselective hydroboration of almost any alkene through the employment of a small selection of highly efficient catalytic methods. Apart from the hydroboration of alkenes, Morken's convergent approach of forming a carbon-carbon bond between in-situ-formed metal-stabilised α-boryl carbanions and vinyl/aryl metal species is highly attractive. The extension of this asymmetric method to forming sp^3–sp^3 carbon–carbon bonds would be extremely powerful. Catalytic asymmetric transformations of boron-containing prochiral substrates, such as asymmetric hydrogenations, asymmetric hydrofunctionalizations and enantiotopic-group-selective coupling methods have also recently become the focus of increased research interest and offer great promise in the field. Methods for the borylative difunctionalization of alkenes are also emerging as important tools owing to the high level of complexity that is introduced in a single transformation. If issues of regio- and enantiocontrol can be addressed, the direct borylation of unactivated C–H bonds will also undoubtedly become an integral method for the synthesis of optically active alkyl boronic esters. Despite the immense progress that has been made since H. C. Brown's seminal publication in 1961, the asymmetric synthesis of secondary and tertiary boronic esters remains a field rich in potential for the development of new

methodologies. The versatility of alkyl boronic esters and their resulting importance in complex molecule synthesis means that the challenge of introducing a carbon–boron bond in a stereodefined and site selective manner will continue to attract great interest from the synthetic chemistry community.

Acknowledgements

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Biographies

Beatrice Collins received her BA and MSci degrees and PhD under the supervision of Professor Matthew J. Gaunt from the University of Cambridge. She then spent two years at the University of Groningen (the Netherlands) undertaking postdoctoral studies with Professor Ben L. Feringa. In 2016 she moved to the group of Professor Varinder K. Aggarwal at the University of Bristol as a postdoctoral research associate, where her current research interests focus on the stereoselective synthesis of alkyl boronic esters.

Dr Claire Margaret Wilson was born in Dublin, Ireland. She graduated from Trinity College Dublin with a BA (Mod) in Medicinal Chemistry, during which she worked as an undergraduate researcher in the group of Prof. Pier-Giorgio Cozzi in the Universita di Bologna, Italy. In 2010 she was awarded an IRCSET Enterprise Fellowship to conduct her PhD studies under the supervision of Prof. Patrick J. Guiry MRIA in University College Dublin. She subsequently took up a position as a Teaching Fellow in Newcastle University, where she worked as a Research Associate in the Northern Institute of

Cancer Research. In 2015, she joined the group of Prof. Varinder Aggarwal FRS as a Research Associate. Dr Wilson is currently a Teaching Fellow in the University of Bath, with her independent research focusing on the synthesis of natural product analogues for the treatment of cancer and cardiovascular disease.

Eddie L. Myers obtained his B.A. in Natural Science from Trinity College Dublin in 2000 and followed that with an M.Sc. in Organic Chemistry while working in the laboratory of Prof Youla Tsantrizos and Prof. Masad Damha at McGill University, Montreal. After completing a Ph.D. at the University of Bristol in the laboratory of Varinder Aggarwal (2006), he pursued postdoctoral work with Ronald Raines at the University of Wisconsin–Madison and then with Dirk Trauner at the University of Munich. In 2012, he took up a position with Wiley-VCH (Weinheim), working in the editorial office of Chemistry–A European Journal. In 2014, he returned to research and the Aggarwal laboratory to take up his current position as Research Officer. His research interests include chemical biology and synthetic transformations involving organoboron compounds.

Varinder K. Aggarwal studied chemistry at Cambridge University and received his Ph.D. in 1986 under the guidance of Dr. Stuart Warren. After postdoctoral studies (1986-1988) under Prof. Gilbert Stork, Columbia University, he returned to the UK as a Lecturer at Bath University. In 1991 he moved to Sheffield University, where he was promoted to Professor in in 1997. In 2000 he moved to Bristol University where he holds the Chair in Synthetic Chemistry. He was elected Fellow of the Royal Society in 2012.

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